"INCIDENCE OF SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS EFFECTS ON HbA1C AND LIPID PROFILE"

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CERTIFICATE

This is to certify that the dissertation entitled "**INCIDENCE OF SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS EFFECTS ON HbA1C AND LIPID PROFILE**" is a bonafide work done by **DR.ARVIND KRISHNAKUMAR**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic year 2012 - 2015

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CONTENTS

LIST OF ABBREVIATIONS

SCHT	**–**	**SUBCLINICAL HYPOTHYROIDISM**
OHT	**–**	**OVERT HYPOTHYROIDISM**
DM	**–**	**DIABETES MELLITUS**
LDL	**–**	**LOW DENSITY LIPOPROTEINS**
HDL	**–**	**HIGH DENSITY LIPOPROTEINS**
VLDL	**–**	**VERY LOW DENSITY LIPOPROTEINS**
CVD	**–**	**CARDIOVASCULAR DISEASE**
T3	**–**	**TRIIODOTHYRONINE**
T4	**–**	**THYROXINE**
TSH	**–**	**THYROID STIMULATING HORMONE/ THYROTROPIN**
TRH	**–**	**THYROID RELEASING HORMONE**
TR	**–**	**THYROID RECEPTORS**
RXR	**–**	**RETINOID X RECEPTORS**

ABSTRACT

INCIDIENCE OF SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS EFFECTS ON HbA1C AND LIPID PROFILE

Arvind Krishnakumar[1], R. Penchalaiah[2]. P Dharmarajan[3]

INTRODUCTION: There is a significant prevalence of thyroid disorders in patients with diabetes mellitus, the most common being subclinical hypothyroidism. The co-existence of subclinical hypothyroidism may alter the glycemic profile and lipid profile that is expected in these patients.

AIM: To determine the incidence of Subclinical Hypothyroidism in patients with Type 2 Diabetes Mellitus. Additionally, to evaluate HbA1C and lipid profile in patients having subclinical Hypothyroidism and Type 2 Diabetes Mellitus and compare with those having only type 2 Diabetes Mellitus.

MATERIALS AND METHODS: Two hundred patients above 40 years diagnosed to have Diabetes Mellitus were subjected to Short Relevant History and Physical Examination as per the questionnaire. Liver and renal function tests, fasting thyroid profile and fasting lipid profile were taken for all patients. Those who had an abnormal liver or renal function test were excluded.

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RESULTS: Subclinical Hypothyroidism was present in 12 percent of cases. Four percent had overt hypothyroidism. Females were significantly higher in proportion than males among those who had subclinical hypothyroidism. The presence of subclinical hypothyroidism was not significantly related to higher levels of HbA1C. The mean HbA1C in the groups with and without subclinical hypothyroidism were 7.93 and 8.53% respectively. There was no significant correlation between duration of diabetes and presence of subclinical hypothyroidism. There was no significant effect on Total and LDL cholesterol, and HDL cholesterol, in patients with subclinical hypothyroidism. There was a significantly higher prevalence of hypertriglyceridemia (13.7% versus 79.2%), and the mean value of serum triglyceride level was 184.4 md/dL in patients with subclinical hypothyroidism, versus 151.3 mg/dL among those with only diabetes.

CONCLUSION: There is a significant increase in the incidence of subclinical hypothyroidism in patients with type 2 diabetes mellitus and this increase is associated with a significant rise in the triglyceride levels. There is no correlation between HbA1C, total cholesterol, and LDL and HDL cholesterol with presence of subclinical hypothyroidism.

KEY WORDS: Subclinical Hypothyroidism, type 2 diabetes mellitus, lipid profile, HbA1C.

INTRODUCTION

Two of the most common endocrinological diseases are Diabetes and Hypothyroidism. Diabetes mellitus is a disorder of glucose metabolism wherein the digested carbohydrates are not metabolised either due to an absolute or relative lack of the hormone insulin, that is derived from the pancreas, or due to a relative peripheral resistance for glucose uptake in tissues like the liver, adipose tissue, and skeletal muscle. Hypothyroidism refers to an absolute or a relative deficiency in the thyroid hormones. Diabetes mellitus is diagnosed using either Random, fasting, or post prandial plasma glucose levels, or with Glycated haemoglobin (HbA1c) levels in a patient. Hypothyroidism may or may not present with signs and symptoms pertaining to the disease. Whether clinically apparent or not, Hypothyroidism is basically a biochemical diagnosis, done with the help of thyroid function tests. Hypothyroidism can be primary, wherein the defect is in the thyroid gland per se, or secondary, wherein the thyroid gland fails to function due to lack of, or an abnormal, stimulation by the pituitary hormone thyrotropin (TSH). Primary diseases are more common than secondary. Hypothyroidism may be subclinical or overt. Since majority of the thyroid hormone triiodothyronine (T3) is formed from peripheral conversion of the thyroid hormone thyroxin (T4) in the tissues, its level in plasma is minimal, and measurement of serum T3 in plasma proves to be a difficult task. Hence,

thyroid gland dysfunction is diagnosed mainly using two parameters – Serum free T4 and serum Thyrotropin (Thyroid Stimulating Hormone; TSH) levels.

Subclinical Hypothyroidism is diagnosed in the presence of an elevated serum TSH with a normal Serum free T4 whereas overt Hypothyroidism is diagnosed when there is an elevated serum TSH with decreased free T4. Subclinical Hypothyroidism may be found in 6-8% women and 3% men. The annual risk of developing subclinical Hypothyroidism is about 4% when there is an associated positive TPO antibody.

There is a significantly higher proportion of individuals who suffer from thyroid dysfunction in the diabetic population when compared to the general population, the most frequent pattern being subclinical Hypothyroidism, and these thyroid disorders are more prevalent in women than in men.

Both Hypothyroidism and Diabetes alter lipid levels and are the leading causes of dyslipidemia in the current era. However the pattern of altered lipid profile varies in the two diseases. Whereas Diabetes causes abnormalities primarily in High density lipoprotein (HDL) fraction of serum cholesterol, Hypothyroidism primarily affects the Low density lipoprotein (LDL) cholesterol. Both disorders can cause an elevation in the serum triglyceride level. It is important to realise these altered lipid profiles in the above two diseases as they pose a significant risk for atherosclerotic

progression and adverse cardiac and vascular outcomes in an individual. However, the lipid profile pattern in patients suffering from both Diabetes and Subclinical Hypothyroidism has not been studied extensively and remains controversial.

Thyroid hormones, in simple terms, act on various tissues of the body, to maintain thermogenesis, energy expenditure, and other metabolic aspects of the human body. Some of the biochemical properties and mechanisms of actions of thyroid hormones are very similar to those of the catecholamines of the autonomic nervous system. Therefore, thyroid dysfunction in a person is likely to alter many metabolic activities in the body. One of the major metabolic pathways that is primarily affected in thyroid dysfunction is that of glucose. Thyroid hormones regulate glucose absorption from the gut, and there is a documented reduction in absorption in hypothyroid patients, therefore one expects a decreased glucose level in these patients. But this is not so. There are many factors that increase the glucose levels in hypothyroid individuals as well. These include an increased peripheral resistance to insulin due to an increase in adipose tissue mass, a decreased expression of glucose receptors in the peripheral tissues, and many more, including altered gene expression for insulin hormone. Hence, the glycemic control in diabetics with Hypothyroidism (overt and subclinical) may not be good

despite strict dietary and lifestyle modifications, and there are conflicting reports regarding this observation.

The consequences of Hypothyroidism are many, majority of them having an effect over the cardiac and vascular system, and many complications overlap with the microvascular and macrovascular complications of Diabetes. It also becomes a significant comorbid condition that hampers the proper management of Diabetes, posing to be a burden for the patient and the doctor. It has also been proved that these consequences can occur in individuals with subclinical Hypothyroidism as well. It is therefore, very important to screen for and detect type 2 Diabetes mellitus patients who have a coexisting subclinical Hypothyroidism and treat them accordingly.

AIMS AND OBJECTIVES

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AIM:

To determine the incidence of Subclinical Hypothyroidism in patients with Type 2 Diabetes Mellitus.

OBJECTIVES:

1. To evaluate HbA1C in patients having Subclinical Hypothyroidism and Type 2 Diabetes Mellitus and compare with those having only type 2 Diabetes Mellitus.
2. To evaluate Lipid profile in patients having Subclinical Hypothyroidism and Type 2 Diabetes Mellitus and compare with those having only type 2 Diabetes Mellitus

REVIEW OF LITERATURE

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HISTORICAL REVIEW

The term ‘Diabetes’ was derived in the second century, coined by Aretaeus (AD 30-90) of Cappadocia. He derived it from the Greek words ‘dia’ and ‘bianeon’ meaning 'through' and ‘to go’ respectively. The words described a siphon that described polyuria.

Diabetes mellitus was also described in the history of Indian literature in the Sanskrit scriptures of Charaka, Susruta and Vaghbata back in the 5^{th} and 6^{th} century BC. They described the sweet taste of urine in polyuric patients and the disease was termed ‘Madhumeha’. They even differentiated the disease into two forms, one affecting older people and who are obese, and the other affecting thin and young people who do not survive long. This description correlated well with the current classification of type 1 and type 2 Diabetes. The term ‘honey urine’ as described in Indian literature referred to the urine of diabetic individuals that was clear, colourless and sweet.

The thyroid gland was first observed by Galen, who initially thought it to be an organ that provided fluid for lubricating the larynx. The term ‘thyroid’ is a Greek terminology coined by Wharton, meaning ‘Shield’, who considered it a gift of nature to females to give the neck a more beautiful look.

The thyroid gland was first described by Andrecos Vesslius as ‘two glands on each side of the laryngeal root which are flesh coloured, large fungus like, and covered with blood vessels’

The isthmus of the thyroid gland was discovered by Eustachius, while Wharton discovered the anatomical site, weight and size in his book Adenographia.

In 1915, a group of physicians in the Mayo Clinic led by Dendall isolated the thyroid hormone thyroxine for the first time, but it was Harrington in 1925 who first determined the chemical constitution of the hormone, and discovered a method of in vitro synthesis of the same.

DIABETES MELLITUS

Diabetes Mellitus is a group of diseases that share the common metabolic defect of hyperglycemia[1]. These diseases differ mainly in the manner in which they produce hyperglycemia. The mechanisms may be genetic, acquired, or environmental. Eventually this leads to decreased secretion of insulin from the pancreas, decreased utilization of glucose in the peripheral tissue and increased hepatic production of glucose

Diabetes mellitus can be broadly classified into

Type 1 Diabetes

Type 2 Diabetes

Gestational Diabetes mellitus

Other specific types of Diabetes[2]

DIAGNOSING DIABETES MELLITUS

Diabetes Mellitus may be suspected clinically when a patient presents at the clinic with classical symptoms of hyperglycemia (blurry vision, increased urine output, thirst, and a recent onset weight loss) and has a random plasma glucose value of 200 mg/dL or higher.

Other diagnostic criteria have been developed based upon the risk for developing retinopathy and the observed association between glucose levels. Fasting plasma glucose values more than or equal to 126 mg/dL, Glycated haemoglobin A1C values more than or equal to 6.5 percent, and two-hour post oral glucose challenge values of more than or equal to 200 mg/dL are associated with an increased prevalence of retinopathy[3].

Not surprisingly, since the different measures of glycemia represent different physiologic phenomena, each of the measures will identify different proportions of the population with Diabetes. For example, the shift from

using the fasting plasma glucose to using A1C to diagnose Diabetes may decrease the proportion of patients identified as having Diabetes[4-6]. As an example, in a study of 6890 adults without a history of Diabetes participating in the National Health and Nutrition Examination Survey (NHANES; 1999 to 2006), the prevalence of Diabetes using A1C versus fasting plasma glucose criteria was 2.3 versus 3.6 percent[4]. Overall, the A1C and fasting plasma glucose criteria resulted in the same classification for 98 percent of the population studied. Similarly, the oral glucose tolerance test (OGTT) identifies different groups than an FPG level.

In 2003, the American Diabetes Association recommended the use of fasting plasma glucose levels or 75g oral glucose tolerance test for diagnosing Diabetes[7]. In 2009, an International Expert Committee recommended using an A1C value of more than or equal to 6.5 percent to diagnose Diabetes[8].

THE ACTION OF THYROID HORMONE

Thyroid hormones are major determinants of metabolic activity in adults, and of the development of the somatic system and the brain in children and infants.Thyroid hormones must be constantly available as they affect the function of virtually all organs / tissues / systems. For a constant and continuous availability, these hormones are stored in large amounts in the thyroid gland. Moreover, thyroid hormone secretion and biosynthesis are

maintained within narrow limits by a very sensitive mechanism that is regulated by even small changes in the concentration of the circulating hormones. There are two major thyroid hormones – Thyroxine (T4) and triiodothyronine (T3). T3 acts in virtually all tissues by altering rates of protein synthesis and substrate turnover primarily by modifying gene transcription[9]. Multiple factors reduce or amplify the action of thyroid hormones. There is an increasing recognition in the extra-nuclear mechanisms of thyroid hormones and these are controlled by interactions with components of the signal transduction system, membrane receptors, and the cell organelles.

The intra nuclear mechanisms of triiodothyronine (T3) depend on four main factors:

1. DNA regulatory elements
2. The availability of the hormone
3. Receptor cofactors
4. Thyroid hormone nuclear receptors (TRs).

The major regulatory element for thyroid hormone synthesis and secretion is the pituitary thyrotropin (TSH). Diffusion is the primary method by which Thyroxine (T4) and T3 in the circulation enter the cells and, in a few specialised tissues, such as the brain, it is by active transport. This is an important fact because alterations in the circulating hormone levels and

subsequently impaired neurologic development in boys has been attributed to an inherited gene defect coding for the MCT8 thyroid transporter. T4, within the cells, can get converted to T3, and this locally produced T3 is the one that majorly binds to the nuclear receptors in the majority of the tissues. This peripheral conversion, or in broader terms extrathyroidal conversion make up about eighty percent of the circulating T3 in human beings, the rest twenty percent is derived from direct thyroidal secretion[10].

T3 can also be regulated at the level of tissues and this is a significant influence on the action of thyroid hormones. The following fractions vary from species to species and from tissue to tissue: 1) Amount of T3 that is produced locally from T4; 2) The amount of locally produced T3 to the number of receptors that is T3 bound. In human beings, around eighty percent of extrathyroidal T3 formed from T4 occurs intracellularly.

There are two Thyroid Receptors (TR) that exist, alpha and beta[9]. Separate genes encode for these two receptors which are located in Chromosomes seventeen and three respectively. The two receptors are similar structurally; but due to the mechanism of alternative splicing, each receptor has multiple subtypes, TR-alpha-1 and TR-alpha-2 and TR-beta-1, TR-beta-2, and TR-beta-3. Triiodothyronine (T3) binds to these Thyroid Receptors, with the exception of TR-alpha-2, and complexes are formed between T3 and TR, these complexes then regulate the specific genes that

respond to thyroid hormone by binding to regulatory proteins. If T3 does not bind to TR, then TR that is not complexed can cause repression of the expressed gene by binding to co-repressors and then to the regulatory zones of the genes.

The TR subtypes contain several distinct regions that bind to DNA, T3, and form polymers with TR molecules, as well as other receptors which bind 9-cis retinoic acid, such as retinoid X receptors (RXRs). The primary functional unit for regulation of the gene responsible for T3 hormone is a TR/RXR heterodimer.Thyroid hormones are themselves the predominant influencing factor on the activity of this particular heterodimer, but the influence of RXR on the nuclear receptor varies depending on its receptor partner.

A large number of regulatory products interact with TRs directly. The 5'-flanking domain (located upstream from the starting site of transcription) of the genes that respond to thyroid hormone containdistinct DNA sequences that alter expression of the gene by binding toheterodimers of TR/RXR.

Thyroid hormone has relevant effects on development of both the nervous system and somatic systems, and these effects occur during both the embryogenic period as well as postnatally during first few years.The thyroid gland of the fetus starts functioning at ten to twelve weeks of gestation, and this is the major source of thyroid hormone in the developing fetus after the

first trimester, during which maternal thyroxine (T4) is the only source. In congenital Hypothyroidism, where the fetus cannot make any hormone, it receives enough T4 for normal in utero development from the mother via the placenta. In severe deficiency of iodine, which can be present when there is a deficiency of iodine or thyroid hormone in both the mother and fetus, development of the fetus is abnormal, and these abnormalities cannot be reversed with hormone replacement therapy postnatally.Pregnant females who are hypothyroid have a higher rate of preterm delivery and miscarriage, and sometimes the offspring are minimally impaired intellectually. Expression of the TR subtypes have similar patterns among different species in which it has been studied, and there is a difference in its expression in the tissues of the fetus and the adult.The first isoform to be expressed is TR-alpha. Later on, TR-beta appears, and this is the time when T3 is produced first. Both the TR isoforms are functional, even though their discrete roles in the fetal development is suggested by their pattern and timing of expression.

Triiodothyronine (T3) acts on different tissues exerting different actions. It is the distribution of TRs and the content of TR isoforms in various tissues as well as differences in the local T3 production that determine the variations in the actions of T3[11].

There are special characteristic variations in the expression of the TR-alpha and TR-beta iso forms in various tissues. Kidney, Muscle, and liver

contain mainly TR-beta, whereas the cardiac myocytes contains similar amounts of TR-alpha and TR-beta. In the brain tissue, it is dominated by TR-alpha, but some regions of the brain contains higher levels of TR-beta-2, especially in the pituitary and the hypothalamus, and this isoform plays a distinct role in negative regulation of genes by T3, such as the those for thyrotropin-releasing hormone (TRH) and the subunits of thyrotropin (TSH). Even inside a tissue (as an example, brain, heart, or bone) there is region- or cell-specific variation of the isoforms of TR, suggesting that the different TR isoforms function differently.

Thyroid receptor gene point mutation experiments and gene knockout experiments performed in mice derive most of what is known about the role of the individual TR isoforms.The mice used in such experiments originate from embryonic stem cells which have mutation or deletion of the genes encoding TR-alpha or TR-beta and the resulting mice have the desireddefect. The function of the gene under study is then determined based on the phenotype of the mice after genetic alterationwhen compared to normal (wild-type) mice, as well as the influence of cofactors. TR-alpha deletionscausereducedgrowth and feeding, decreased bone mineralisation, decreased basal body temperature, and decreased heart rate. Low thyroxine (T4) and serum TSH are the thyroid function changes that are observed. Mice that are heterozygous for dominantly negative point mutations, similar to the

mutationsseen in TR-beta gene associated with resistance to thyroid hormone, have a phenotype generally similar to the TR-alpha homozygous deletions. Other abnormalities that are detected in mice with dominant negative TR-alpha mutations are nervous system developmental defects, impairment in adaptation to changes in temperature, and, obesity and impairment of lipolysis as observed in one TR-alpha mutation. Many case series have mentioned family members where there is resistance to thyroid hormone which is associated with TR-alpha gene mutations. These patients have low plasma T4, normal or high plasma T3, and normal to high plasma TSH, with signs of Hypothyroidism including abnormality in development of bony tissue, constipation, and decreased or altered metabolic activity. Inactivating the gene encoding TR-beta is linked with hyperplastic thyroidglands, high plasma T4 levels, and inappropriately normal plasma TSH levels, similar to the features of those patients with thyroid hormone resistance associated with a TR-beta gene mutation. Other features include deafness, which has a good correlation with the expression of TR-beta in the cochlea in normal developing mice, and increased heart rate. Survival is not impaired. Heterozygous point mutations in the TR-beta gene, similar to those with resistance to thyroid hormone, have a phenotype similar to mice homozygous for deletion of the gene encoding TR-beta.

Both TSH secretion in response to Hypothyroidism and suppression of secretion of TSH by T3 is defective in these mice. These observations suggest that TR-beta has a crucial part in increase of TSH independent of ligands, as well as in suppression of TSH mediated by T3.Mice in which deletions of both TR-alpha and TR-beta genes are present have significant hyperplastic thyroid tissue and elevated levels of plasma T4 (12 times more than usual), T3 (31 times more than usual), and TSH (up to 165 times more than usual) [12]. They have poor growth, the mRNA for the growth hormone as well as the hormone itself is reduced in quantity in the pituitary gland, and they have low plasma insulin-like growth factor-1 levels. Bone development and mineralisation are impaired, and the epiphyseal plates are not organised well. Fertility is severely defective in the females. Survival decreases; about 32 percent of the mice expire by three quarters years of age, as compared with nil deaths in the wild-type mice of the same age. Relevant target organs for thyroid hormones during stages of growth include inner ear, retina, small intestine, pituitary, and bone.

Repression or activation of genes that are mediated by TRs also involve an interaction of other protein cofactors with TRs. These proteins, also labelled corepressors and coactivators, inhibit or activate interaction of the basal transcription mechanism with TR. Many cofactors interact with retinoid and steroid hormone receptors additional to TRs. Examples of

corepressors are NCoR (nuclear corepressor) and SMRT (silencing mediator of retinoid and thyroid receptors). Examples of coactivators are SRC (steroid receptor coactivators) and CBP (CREB [cAMP responding element-binding protein] binding - protein). In general, corepressors bind to TR when T3 is not present, repressing the expression of the target gene. When T3 binds to TR, this replaces the corepressor that is bound to TR and provokes binding of coactivator to activate the gene. The TR mutations in association with thyroid hormone resistance generally result in irreversible interactions with corepressors that do not get replaced by the addition of ligand, T3. In mouse models of thyroid hormone resistance with a TR-beta genetic mutation, crossing with a mouse expressing a mutated NCoR that does not bind to TR results in a partial "rescue" of the resistance phenotype. This finding indicates that irreversible binding of corepressor to the mutant TR is a crucial mechanism of the thyroid hormone resistance phenotype.

The observations of studies in animals and humans indicate that these receptor coactivators and corepressors play crucial roles in hormone action and development. Knockout of the CBP and SRC genes is fatal in the neonates and the fetus. These findings indicate the significant nature of these cofactors for development, but do not give data on which genes are most affected when the cofactors are not present. An example of the role of a cofactor in thyroid hormone regulation is SRC. SRC gene deleted mice have

elevated plasma TSH and T4 levels, which rise rapidly in response to Hypothyroidism but do not come down as usual in response to exogenously administered T3.

About 11 percent of individuals with the classical clinical features of thyroid hormone resistance do not have mutant TRs, and instead may have mutant cofactor genes. All genes that are controlled by T3 have DNA sequences that are distinct and interact with TR with great affinity[9]. Most of these sequences, known as thyroid hormone-response elements, consist of tandem arrangement of two hexamer (or octamer) motifs with a consensus sequence of AGGTCA to which T3-TR / retinoid X receptor (RXR) heteromers bind, separated by four base pairs. Response elements are present in the 5'-flanking regulatory zone of the DNA, but can be located throughout the gene including in flanking sequences and introns. The structures of response elements that lead to T3-dependant gene promotion have been well documented, and preferentially bind T3-TR/RXR heteromers. A single octameric sequence, TAAGGTCA, can also bind TR-TR dimers and promote gene regulation. Response elements that confer gene repression have been more difficult to detect, and few appear to bind only T3-TR monomers. It is possible that interaction with other transcription factors is involved in negative regulation. In all genes regulated by T3 via modification of transcription, it should be possible to detect a gene sequence that can be

linked to this regulation. With the availability of gene sequence data from the human genome project, it is plausible to detect genes regulated by T3 based upon inspecting the sequences. Direct methods to detect sequences that bind receptors exist and these have been used to detect genes regulated by related hormones, such as estrogen.

Conversion of the prohormone T4 to the active hormone T3 and conversion of T3 to diiodothyronines is done by the deiodinases, which are expressed in a development - specific and tissue-specific pattern. Type 1 5'-deiodinase (D1) is found mainly in muscle, kidneys and liver. In rats, circulating T3 is obtained from activity of this enzyme. D1 activity is reduced in Hypothyroidism. Type 2 5'-deiodinase (D2) is seen predominantly in cerebral cortex, pituitary and brown fat in rats. It is more widely present in humans, including the skeletal muscle, heart and thyroid, and is the major source of circulating T3 in humans. D2 activity is elevated in Hypothyroidism and deficiency of iodine. Type 3 5 - deiodinase (D3) inhibits T4 and is present in skin, skeletal muscle, developing brain and placenta.In terms of development, expression of this deiodinase occurs first, and its expression decreases as the other two deiodinases are expressed more. D3 activity is also crucial to regulate thyroid hormone action in development of the sensory system, especially of the inner ear. Type 3 deiodinase (D3) appears to have a critical part in the maturation and function of the thyroid

axis. This was demonstrated by a D3 gene deleted mouse model where central Hypothyroidism following neonatal thyrotoxicosis was seen.

Thyroid hormones predominantly target are the heart, the metabolic regulation and the skeleton. Infants with congenital Hypothyroidism who are not treated have disordered and delayed epiphyseal development and have poor growth, as do some infants with thyroid hormone resistance[13]. Abnormalities in development of bone is also a prominent feature of thyroid hormone receptor TR-alpha and combined TR-alpha / beta knockout mice. All TR isoforms have expressions in the bone, and probablyinteract with other nuclear receptors including those for retinoids and Vitamin D. However, in the bone, relatively few genes regulated by triiodothyronine (T3) have been identified. Plasma levels of osteocalcin have a correlation with thyroid function, and levels of mRNA coding for osteocalcin in bone are stimulated by T3 in a domain-specific pattern, similar to those areas such as the pelvis that are most susceptible to osteoporosis in patients with hyperthyroidism. Bone loss mediated by Thyroid hormone is due to enhanced catecholamine activity due to TR-alpha function.

The heart is a predominant target for thyroid hormone action[14]. Most patients with thyroid hormone resistance have tachycardia, indicating no cardiac resistance to T3. This observation is consistent with the fact that these patients have TR-beta mutations, since mice with TR-beta deletions do not

show cardiac resistance to T3. In contrast, mice with TR - alpha deletions have bradycardia. This is also consistent with the absence of tachycardia in patients treated with selective TR - beta agonists. Thyroid hormone is a regulator of rate of metabolism and is associated with body weight changes. Animal models have demonstrated that TR - alpha is important for thyroid hormone-mediated enhancement of adrenergic action. Humans with thyroid hormone resistance associated with TR - beta mutations and elevated thyroid hormone levels have increased stimulation of TR - alpha. The metabolic phenotype of increased - TR alpha stimulation is increased feeding and increased fatty acid oxidation. There is a direct connection between response of subcutaneous fat to stimulation by the adrenergic system and the thyroid status. The regulation of glucose uptake is more complex, but thyroid hormone promotes glucose uptake and polymorphisms in the D2 gene have been associated with glucose intolerance. Impairment of mitochondrial oxidative metabolism, as is seen in type 2 diabetes and the metabolic syndrome, may be linked to some individuals to reduced thyroid hormone action. Thyroid hormone also regulates metabolism by interaction with other metabolic nuclear receptors such asliver X receptor (LXR) and peroxisome proliferator - activated receptor (PPAR)-alpha.

Many drugs have been reported that can alter thyroxine (T4) absorption and metabolism[14]. Agonists for retinoic acid receptor (RAR) and

retinoid X receptor (RXR), retinoids and rexinoids, suppress thyrotropin (TSH) and can produce central Hypothyroidism in some patients. Agents that have been shown to interfere with thyroid hormone action include smoking cigarettes, and a range of environmental agents, especially polychlorinated biphenyls (PCBs). It is the sodium – iodide symporter, abbreviated as NIS, which concentrates iodine in the thyroid gland. Agents that block NIS and iodine concentration include perchlorate, a water and food contaminating agent in some areas, and thiocyanate, an agent that is a component of cigarette smoke, and is also found in polluted water. Although soy is also estimated to be a blocker of NIS, there is no evidence that is convincing enough to prove that isoflavones have an in vivo inhibition of the action of thyroid hormones. The protein, however, can inhibit the intestinal absorption of T4, this step being a crucial one in children less than 1 year with congenital Hypothyroidism who are receiving some sort of soy-based feeds and taking replacement therapy for thyroid hormones orally.

T3 and T4 act on virtually all organs and tissues in the body. They act on the following processes:

Effects on the cardiovascular system – there is a direct catecholaminomimetic action of thyroid hormones on the heart, which leads to an increase in the cardiac output. This in turn rises the heart rate and pulse pressure. Moreover there is a cutaneous vasodilation due to the decreased

peripheral resistance which activates heat dissipating mechanisms and leads to a slight increase in body temperature. All these actions ultimately lead to a decreased circulation time. These actions are not due to T3 from myocytes as T3 is not produced from T4 in these cells, but it is the circulating T3 that enters the myocytes that is the cause of its action. These circulating hormones enter the muscle cells, combines with thyroid hormone receptors and then enters the nucleus. In the nucleus it promotes or inhibits the expression of genes. The genes that are inhibited include those for Sodium-calcium exchanger, beta-myosin heavy chain, T3 nuclear receptors, and phospholamban. The genes that are promoted include Potassium channels, alpha-myosin heavy chain, sodium-potassium ATPase, sarcoplasmic reticulum Calcium ATPase and G proteins. However, the overall result is an increase in the force of contraction and heart rate. There are two myosin heavy chain isoforms in the heart, the beta - MHC and the alpha - MHC. These isoforms are coded by two genes that are highly homogenous and are located on the short arm of chromosome 17. There are two pairs of light chains and two pairs of heavy chains in each myosin molecule. In the myosin containing beta-MHC, there is less of ATPase activity compared to the myosin containing alpha - MHC. The alpha - MHC is the predominant isoform in the atria of adults and this increases the speed of contraction. Its levels are increased by therapy with thyroid hormones. On the other hand,

their expression is depressed in Hypothyroidism, whereas that of beta-MHC is enhanced.

Effects on the Nervous system – the thyroid hormones cause general activation of the nervous system. The cerebrospinal fluid of hypothyroid patients show an elevated protein level, moreover they have a slow mentation. On administering thyroid hormones in such patients, these changes are reversed. However, the oxygen and glucose consumption as well as the cerebral blood flow are normal in adult hyperthyroidism and Hypothyroidism. Thyroid hormones, in the central nervous system, are found in numerous locations of the gray matter. The astrocytes in the central nervous system are responsible for the peripheral conversion of T4 to T3, and it is observed that a sharp rise in the brain dopaminergic (D2) activity occurs after thyroidectomy, this is rapidly reversed after a single intravenous dose of T3 within 4 hours. There is a catecholamine stimulant activity which causes activation of the reticular activating system. Thyroid hormones also prominently affects the development of the brain, especially of the basal ganglia and the cerebral cortex. Thyroid hormones also affect the cochlea. Subsequently, deficiency of thyroid hormone during the growing phase in a child would lead to deaf-mutism, mental retardation and motor rigidity. The effects of thyroid hormones on reflexes are complex. In hyperthyroidism, the

stretch reflex reaction time is shortened, while the converse happens in Hypothyroidism.

The actions of catecholamines and the thyroid hormones are closely related. The toxicity of these catecholamines is increased in rats treated with T4. In hyperthyroidism, certain affects like tremors, cardiovascular effects, and sweating can be reduced by sympathectomy or drugs like propranolol. Beta blockers are also used in the treatment of thyroid storm.

Effects on skeletal muscle – In hyperthyroidism, an entity called thyrotoxic myopathy occurs, which leads to muscle weakness. This is in part due to increased protein catabolism. Like in the myocytes, thyroid hormones play acrucial role in expression of genesof certain proteins, for example, the myosin heavy chain. Hypothyroidism may also be associated with muscle weakness, stiffness and cramps.

Carbohydrate metabolism – thyroid hormones promote metabolism of carbohydrates in the body by stimulating oxidative phosphorylation and the tricarboxylic acid cycle. However, their more pronounced effect is in the gut where it stimulates carbohydrate absorption. This action is also independent of its calorigenic action.

Effects on cholesterol metabolism – thyroid hormones cause a decrease in the serum cholesterol levels. This drop in the plasma cholesterol

is known to occur even before the rise of the metabolic rate. There is an increase in the number of receptors for low density lipoprotein in the liver, which leads to an increased clearance of the circulating cholesterol by the liver. This action of the thyroid hormone, however, is independent of its oxygen consumption stimulatory action.

Effects on growth – for normal growth and skeletal maturation, thyroid hormones are an essential requirement. Bone growth is delayed and epiphyseal closure is slowed in hypothyroid children. Secretion of growth hormone is also depressed in these patients, which further worsens the effects of Hypothyroidism.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism (SCHT) is only a biochemical definition and not a clinical one. The term itself implies that the patient does not have any overt specific symptoms characteristic of Hypothyroidism. Biochemically, it is defined as an elevated serum thyrotropin in the presence of a normal serum free thyroxine (free T4). A few patients with SCHT do present with certain subtle symptoms of Hypothyroidism, but there is no definite clinical criteria and efforts to clinically diagnose patients with SCHT has been in vain[16, 17]. Thus, SCHT is a laboratory diagnosis, not a clinical one.

In the presence of a low serum free T4 and an elevated serum TSH level, one can put a diagnosis of overt Hypothyroidism. Overt Hypothyroidism, is also defined based on laboratory values although almost all patients present with obvious clinical signs and symptoms of the disease.

	Low TSH	Normal TSH	High TSH
High Free T4	Overt Hyperthyroidism	——	Secondary Hyperthyroidism
Normal Free T4	Subclinical Hyperthyroidism	**NORMAL**	Subclinical Hypothyroidism
Low Free T4	Secondary Hypothyroidism	——	Overt Hypothyroidism

In studies based on the general population, the range of prevalence of SCHT is from 3 to 16 percent[18-22]. In a survey conducted by the United States National Health and Examination (NHANES 3), 4.2 percentageof 16,534 individuals were diagnosed to haveSCHT[16]. The study had excluded patients who were previously diagnosed to have Hypothyroidism and those who are undergoing treatment for the same. The prevalence increased with an increase in the age. The disease was also more prevalent in females when compared to males and was more in the whites when compared to blacks. The drawback

was that the prevalence strongly correlated with the upper level of normal TSH values.

Subclinical Hypothyroidism in Europe was area - dependant. This could be explained by the fact that there were many regions of iodine deficiency in the country, and there was a gross variability in the intake of iodine. In a report, the prevalence of SCHTwas ranging from 23.9 % in regions deficient in iodine to 4.3% in one region having an abundance in iodine intake, in spite of a similarity in the prevalence of individuals with an elevated serum concentrations of antibodies to thyroid peroxidase (anti-TPO) [24].

In the Indian subcontinent, the prevalence of Subclinical Hypothyroidism has been evaluated in India, Pakistan and Bangladesh. In a Municipal Hospital in Mumbai, 237 subjects from paramedical personnel registry were selected for a cross sectional observational study with an aim of defining the normal ranges for thyroid hormones and thyrotropin, and to study the prevalence of SCHT in paramedical population in Mumbai[25]. The study found a prevalence of SCHT in 11.3% cases, with a female: male ratio of 4: 1. Other studies in India include that by Dr Meena Desai *et al*. on first degree relatives of children with thyroiditis, Unnikrishnan *et al.* on 971 adults In cochin[26], and Abraham *et al.* on prevalence in females in Puducherry[27], all of them had Subclinical Hypothyroidism being the most common thyroid

disorder and there was a higher prevalence of the disease in females. JM Alam *et al.* assessed 230 patients (98 males, 132 females) in a general hospital in Karachi, in the age groups of 19 to 66 years, and found an increased prevalence of Subclinical Hypothyroidism(13.7%)compared to subclinical hyperthyroidism (7.57%) and an increased prevalence in the age groups 31 to 66 years and in females (Female : Male = 2 : 1)[28]. The higher prevalence of the disease compared to NHANES is probably due to the increased rate of endemic goitre in these regions and the pure lack of awareness of the disease and its preventive methods.

ETIOLOGY OF SUBCLINICAL HYPOTHYROIDISM

Overt Hypothyroidism and SCHT have exactly the same etiology and they include

Chronic autoimmune thyroiditis

Persistent TSH increase in subacute thyroiditis

Postpartum thyroiditis

Painless thyroiditis

After thyroidectomy / radioactive iodinetherapy / external radiotherapy of head and neck

Drug induced Hypothyroidism

Inadequate replacement therapy for overt Hypothyroidism

Thyroid infiltration disorders

Amyloidosis

Sarcoidosis

Hemochromatosis

Riedel's thyroiditis

Cystinosis

AIDS

Primary thyroid lymphoma

Toxic substances.

Majority of the patients suffer from chronic autoimmune thyroiditis, also called Hashimoto's thyroiditis, with elevated serum concentrations of antibodies to the enzyme thyroid peroxidase[29]. Other major causes include prior ablative or antithyroid drug therapy for hyperthyroidism. Drugs causing Hypothyroidism include amiodarone, radiographic contrast agents, lithium, interferonalpha, aminoglutetimide, ethionamide, sulphonamides, and sulfonylureas.

DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM

Subclinical Hypothyroidism is only based on laboratory testing and there is no clinical criteria or diagnosis for SCHT. Subclinical Hypothyroidism may occur in the absence or presence of clinical features of Hypothyroidism. Most patients are asymptomatic witha low level of serum TSH (<10mU/L) [30].

Most of the institutes in the world use serum TSH as a valid screening test for thyroid disorder. An elevation in the serum TSH concentration should probe the clinician to repeat the serum TSH concentration along with a serum free thyroxine (serum FT4) to diagnose SCHT.The serum TSH should also be repeated again after 1 to 3 months for confirmation of the diagnosis and to rule out transient temporary elevations. In certain conditions like infertility or pregnancy, or conditions where there can be a strong reason to start treatment, one may start the patient on T4 replacement therapy if the repeat TSH that is done along with T4 remains increased.

For pregnant women, elevations in TSH should be defined using trimester-specific TSH reference ranges. For nonpregnant adults, a high serum TSH is by definition, a TSH concentration above 4 to 5 mU/L, the upper limit of normal reference range that is considered in most reference laboratories. There is a lot of controversy on the ranges of TSH level. Some experts have mentioned that only 2.5 or 3 mU/L in healthy individuals

without thyroid disease should be considered as the true upper limit, while others are of the opinion that the serum TSH distribution changesto an upper level as the age advances, independent of the presence or absence of antithyroid antibodies[31].

Sometimes patients may have an elevated TSH values in spite of a completely normal thyroid gland. Some of the important explanations are:

1. During recovery from a critical illness that is not related to the thyroid, where a period of suppression of TSH is followed by a transient increase in serum TSH.
2. After a hyperthyroid phase of any form of thyroiditis – postpartum or subacute.
3. Variability in the assays
4. Heterophilic antibodies[32]
5. Rheumatoid factor positivity[32]
6. Autoantibodies to TSH which create macro-TSH[33]
7. Untreated adrenal insufficiency
8. TSH producing pituitary adenomas
9. Central Hypothyroidism

A Heterophilic antibody maybe interfering with immunometric assays used to measure the thyroid hormones[32]. These cause a falsely elevated reading in TSH value. Rarely, Heterophilic antibodies block binding of one

of the mouse monoclonal antibodies to TSH and result in spuriously low readings for TSH. Non-linearity with dilution suggests interference. Addition of nonimmune homologous mouse immunoglobulins has reduced this type of assay interference. Commercial assays exist for detecting human anti-mouse antibodies. Macro - TSH are antigen antibody complexes that are formed by the reaction with TSH and anti-TSH antibodies. These complexes are of the IgG type, and they lack the biologic activity of TSH, but they can still react with immunometric assays, causing an elevation in the TSH, even in euthyroid individuals[33]. Anti-TSH antibodies can be detected by removal of the IgG-TSH complexes with polyethylene glycol or protein A or G, then repeating the assay on the immunsubtracted sera. In patients with resistance to the actions of thyroid hormone, or in adenomas of the pituitary gland that secrete TSH, an elevation in TSH has been shown to have an association with an elevation in serum Free T3 and/or T4 concentrations. In contrast, patients with SCHT have normal free T4 levels.

Secondary to an alteration in TSH receptor, the patient's thyroid gland can develop resistance to TSH – these patients a high serum TSH concentration with low free T3 or T4. In Central Hypothyroidism, twenty five percent of the enrolled individuals have anelevated serum TSH (upto about 10 mU/L) and a low Free T4.

CONSEQUENCES OF SUBCLINICAL HYPOTHYROIDISM

A good number of patients with SCHT subsequently progress to overt clinical hypothyroidism. Following nearly ten to twenty years of follow - up in studies, new onset overt Hypothyroidism occurs in approximately 32 to 54 percent[34-36]. This risk of development of clinical Hypothyroidism is related to the concentration of serum thyrotropin at the beginning of most studies, the risk being higher in the presence of antibodies to thyroid peroxidase (anti-TPO) and with TSH values above 12 mU/L. In one study, 1710 individuals were studied for 21 years, and females who had both the presence of antibodies against thyroid peroxidase and a high initial TSH value progressed to clinical Hypothyroidism at 4.2% every year[28]. A study that involved 83 women were followed up for 9.1 years, and the total percentage of patients who progressed to overt Hypothyroidism was one% for individuals with a TSH concentrations at the beginning of study being less than 4 to 6 mU/L[34].

Another factor that determines the risk of progression to OHT is the underlying thyroid disease[36]. Those individuals who have received either an external high-dose radiotherapy or therapy with radioiodine, and those patients with an underlying autoimmune disease are the ones at highest risk to progress to OHT. On the other hand, Subclinical Hypothyroidism will most likely be expected to persist in patients who had been exposed to

external radiotherapy during childhood, and in individuals after thyroid surgery, where the surgery has been performed for an indication other than hyperthyroidism.

Some patients with SCHT spontaneously recover, but the frequency at which this occurs is not known[34]. In an observation of 422, 242 persons without known thyroid disease, serum TSH was elevated (5.5 to ≤10 mU/L) in 3 percent[37]. During the five-year follow-up period, TSH levels became normal in the absence of treatment in 62 percent of patients. Return of serum TSH concentrations to normal levels is expected within the 1st 2 years after the diagnosis of SCHT, if serum TSH levels <8mU/I, and if individuals are tested negative for Anti-TPO antibodies.

Overt Hypothyroidism may be associated with an increased risk of cardiovascular disease (CVD). In patients with Subclinical Hypothyroidism, the information is controversial, mostly due to variations in sample size and structure and the type of study. Some[38, 39], but not all[40], descriptive studies have reported a higher chance of cardiac disease in patients with SCHT. A meta-analysis of information obtained from six observational studies (25,976 enrolments, 2021 with SCHT) shows a characteristic trend of higher risk of fatal and nonfatal cardiac events (non fatal myocardial infarction, death due to cardiac disease, hospitalisation for angina or coronary revascularisation) at a higher concentration of serum thyrotropin[41]. Participants with serum

thyrotropin levels more than or equal to 8 mU/L had a higher rate of cardiac event when compared to individuals with a euthyroid status (38.5 versus 20.4 event / 1000 person years, hazard ratio 1.88, 95% confidence interval 1.29-2.81). On the other hand, mild increase in thyrotropin (4.6 to 6.8 mU/L) did not have an increased risk (HR 1.10, 95% CI 0.95-1.42). The estimation of risk had no variations based on presence of pre-existing cardiac disease, gender or age.

In another meta-analysis from seven observational cohort reports (25,380 individuals, 2069 with SCHT), analysing the data revealed that there was a significantly higher risk of developing cardiac failure with increased TSH concentrations[42]. Comparing to patients with normal thyroid status, individuals with a thyrotropin level between 11 and 20 mU/L had significantly higher rate of developing heart failure (41 events in 225 participants (18.2%) against 1763 patients in 22,673 controls (7.9%), HR 1.85, 95% CI 1.26-2.73. The higher incidence of heart failure in those with a serum thyrotropin between 6.9 and 9.8 mU/L was not significant statistically (55patients in 423individuals [12.9 %], and mild thyrotropin rise (4.6 to 6.8 mU/L) did not have any significant rise in risk.

Some, but not all, studies show a link between thyroid dysfunction and lipid profile, especially the LDL and total cholesterol concentrations. In a large prospective study (25,863individuals, mean age 55 years), individuals

who had a thyrotropin level between 5.0 and 9.9 mU/L had a significant mean cholesterol levels that were higher than individuals with a thyrotropin level less than 5.0 mU/L (224 against 213 mg/dL). The drawback of this study was, that there was no adjustment for age for the cholesterol levels. Moreover, whether the increased levels is clinically significant in relation to risk of cardiac disease or not is not known.

In few, but not all, reports, individuals with SCHT have a higher chance of mortality due to any cause. In a meta-analysis of data from 12 observational reports, the incidence of mortality due to heart disease increased with higher levels of thyrotropin and was higher in patients with thyrotropin levels more than or equal to 9 mU/L[41]. On the other hand, mild rise in thyrotropin (4.6 to 6.8 mU/L) did not have an increased incidence of cardiovascular events. The incidence of all-cause mortality was insignificant in both the groups. In one observational study that was part of the meta-analysis, individuals in the geriatric age group (age > 80 years) who were suffering from SCHT and not taken treatment, and with thyrotropin levels between 4.7 and 9.9 mU/L, had a reduced incidence of death due to heart disease or other causes compared to the general population[43]. Similar observations were seen in a study from Denmark; Subclinical Hypothyroidism with a TSH of 5 to 10 mIU/L had a reduced incidence of death due to any cause. However, a prospective cohort study from the United

States with older individuals with untreated SCHT had neither a higher nor a lower rate of mortality over a mean follow - up time of five years.

In another cross-sectional study, non-alcoholic fatty liver disease (NAFLD) was compared to serum TSH levels. Thirty and 36 percent of individuals with subclinical or overt Hypothyroidism, respectively, had typical ultrasonographic findings of NAFLD (versus 20 percent of controls) while 20 and 26 percent of individuals with subclinical or overt Hypothyroidism had abnormal liver enzymes.

Neurological and psychiatric diseases may also be associated with SCHT. However one study conducted in the United Kingdom on patients did not show any significant correlation between SCHT and psychiatric disease like depression or anxiety.

Other cardiovascular risk factors and end points may also be associated with SCHT. This includes inflammatory markers, functioning of the endothelium and thickening of the intima media of the carotid.There are reports of patients with SCHT developing increased vascular resistance and diastolic dysfunction, similar to development of the same in OHT. On the other hand, a report showed no abnormality in the function or the mass of the left ventricle in elevated serum thyrotropin levels.

In some, but not all, studies in middle-aged adults, increasing serum TSH concentrations within the normal range or slightly above normal were associated with a modest increase in body weight. In older women (> 65 years), Subclinical Hypothyroidism (mean TSH 6.7 mU/L) compared with euthyroidism (TSH 2.2 mU/L) was associated with a slightly higher baseline weight (0.51 kg higher baseline weight per 1 mU/L higher TSH level) but not with weight change over time. There was no relationship between TSH and weight in older men.

In another study, 22 out of 34 individuals (65%) with SCHT have an increased rate of neurological and muscular features like fatigue and cramps, when compared to 7 out of 45subjects with normal levels (15%). In contrast, a report involving 2050 patients aged above 60 years showed that functional mobility was worse in those with normal range of thyroid hormones than those with mild elevations of thyrotropin levels[44].

Executive functioning and verbal memory may also be affected in patients with SCHT. Correction of thyroid status with replacement therapy caused an improvement of these functions. More than a general slowing in cognition, these defects were believed to be an abnormality in the functioning of the hippocampus.

In another study of the general population, the incidence of Alzheimer's disease was higher in women with SCHT. The incidence for the same was not significantly high in men with SCHT.

Subclinical Hypothyroidism is associated with a higher risk of thrombosis of the deep veins of the legs in a pilot study.

Another study showed dysfunctioning of the Sphincter of Oddi leading to a higher incidence of stones in the common bile duct in patients with SCHT[38].

One report studied the treatment of iron deficiency anemia on patients with SCHT. It was observed that the rise in Haemoglobin was more in patients when they were given replacement therapy for both iron and thyroxine than with replacement therapy with iron alone[38].

Presence of SCHT in pregnancy confers a risk, and it is observed that there is an increased rate of low birth weight and miscarriages of the offspring[38].

EFFECTS OF THYROID HORMONE REPLACEMENT

The most important dilemma for clinicians when managing Subclinical Hypothyroidism is to whether to actually treat them with hormone replacement therapy or not.Since there is a risk of development of OHT in these patients, certain experts favour therapy of SCHT, especially when the

level of thyrotropin goes beyond 9 mU/L. In contrast, treating patients with mild elevations of thyrotropin is still a question of doubt, and this is stratified by the fact that there is no wide-scale study to prove any benefit in treating them.

The studies that have observed any relation between improved symptoms of Hypothyroidism and T4 replacement have varying sample sizes and structures, and different end targets, and so they naturally have conflicting results. In few studies, replacement with thyroxine showed an improvement in symptoms of Hypothyroidism and cognition, especially in patients with an initial serum thyrotropin level more than 10 mU/L. A meta-analysis of 13 observational studies (ten studies used patients with thyrotropin levels less than 14 mU/L), showed no difference in the symptoms and signs of Hypothyroidism nor any differences in adverse effects and quality of life between cases and controls[44].

Other following randomized controlled studies that were not part of the meta-analysis mentioned above evaluated the consequences of thyroxine replacement therapy on symptoms of Hypothyroidism and cognition, and these did not show any benefit on treatment. In a double blind study, 200 patients with serum thyrotropinaround 3.6to15.7 mU/L were treated with 100 micrograms of T4 per day. The results showed a lower incidence of fatigue (90% reduction), but other symptoms as well as quality of life did not have

any improvements.Some patients even developed thyrotropin levels less than normal levels after therapy.

The effect of Thyroxine replacement therapy on cognition was evaluated in one randomised control study. 95 patients more than or equal to 65 years with a serum thyrotropin level more than 5.4 mU/L were observed and a mini mental status score was used to analyse cognition after 6 to 12 months of therapy. Eighty four percent patients achieved normalization of thyroid function after a year of therapy.In the study, however, cognition did not improve significantly even after hormone replacement for 1 year. The trial had many limitations. There was a high rate of drop outs, and fifty percent individuals in the placebo group spontaneously recovered. Despite these limitations, the results of the meta-analysis and subsequent trials, in which most patients had TSH <10 mU/L, suggest that treatment of SCHT with thyroxine does not result in clinically significant improvement in quality of life, depression, and cognition.

In patients with SCHT and goitre, T4 treatment may decrease the size of the goitre. As an example, in a study of 13 patients with Subclinical Hypothyroidism, therapy with T4 had a significant reduction (median 80 percent) in thyroid volume determined by ultrasound.

Although T4 replacement has been shown to correct a lot of risk factors for cardiac disease and endpoints in cardiovascular disease in patients

with Subclinical Hypothyroidism, including endothelial function, carotid intima media thickness, dyslipidemia, markers of inflammation, vascular smooth muscle proliferation, vascular reactivity, and ventricular function, there is limited date regarding the relation between thyroxine therapy and reduction in adverse cardiac outcomes. In astudy by the United Kingdom General Practitioner Research Database, ischemic heart disease events were uncommon among those patients aged 41 to 69 years treated with levothyroxine (69 events in 1635 treated patients [4.3%] against 96 events in 1458 untreated patients [6.7%], hazard ratio [HR] 0.62 [95% CI 0.38-0.94]). However, in individuals over age 69 years there wasn't any benefit intherapy (103 events in 818 treated individuals [12.8%] against 89 events in 824 untreated patients [10.8%], HR 0.98). The incidence of adverse cardiovascular outcomes associated with overtreatment after thyroxine is administered, especially in elder individuals, is not known. Thus, more clinical trials need to be conducted to analyse whether thyroxine replacement therapy reduces adverse cardiac outcomes in patients with SCHT.

In the meta-analysis of 11 clinical trials (eighttrials with thyrotropin levels less than 15 mU/L) described above, six of the trials analysed lipid levels after therapy of SCHT with levothyroxine. There were no significant effects of T4 replacement on total cholesterol, triglycerides,apolipoprotein A

and B, lipoprotein (a), low-density lipoprotein (LDL)cholesterol, or high-density lipoprotein (HDL)cholesterol.

In many studies on individuals with SCHT given thyroxine therapy compared with placebo, there was a significant reduction in serum apoprotein B-100 and total and LDL cholesterol levels. In contrast, there was no differences in the levels in serum lipoprotein (a), triglycerides and HDL cholesterol levels. All these studies included individuals with serum thyrotropin levels > 10 mU/L.

THYROID DISEASE AND DIABETES MELLITUS

The prevalence of thyroid disorders is more in patients with Diabetes than in those without, and more so in type 1 Diabetes than in type 2 Diabetes mellitus[45]. In the Diabetes Control and Complications trial, 58 patients having type 1 Diabetes mellitus, out of which were 33 women and 27 men, were enlisted at University of Tennessee Health Centre. These patients were subjected to thyroid function tests once yearly and Anti-TPO antibodies every four years and were followed up for a period of 18 years. It was found that 18 patients had Hypothyroidism, which was more in females (41%) than males (19%) [46]. The risk of developing hypothyroidism was more in those with positive anti - TPO antibodies, thereby indicating that thyroid dysfunction in such patients have an autoimmune etiology. This validated the use of TPO antibodies as a screening test to predict the occurrence of

Hypothyroidism in type 1 Diabetes, with a positive predictive value of 67%. Despite this association, annual measurement of TSH still remains the best screening test for thyroid dysfunction. Screening for thyroid disease has been approved by the American college of physicians for which guidelines have been set by the same. Screening is not warranted for women under 50 years and men because of its low frequency. But since patients with type 1 Diabetes mellitus have thyroid dysfunction at an earlier age, these screening tests cannot be applied if the individuals have type 1 diabetes. The prevalence of hyperthyroidism, however, was much lower than previously reported.

The prevalence of thyroid disorders is higher in type 2 diabetes as well. In more than 300 patients of type 2 Diabetes, a screening test for thyroid dysfunction was performed, in a clinic in Segovia, Spain[47]. It was found that thyroid dysfunction was seen in 32.4% patients, out of which overt Hypothyroidism was the most frequent thyroid disorder with a prevalence of 15.1%, followed by subclinical hyperthyroidism (10.7%). However, there was no significant correlation between thyroid dysfunction and glycemic profile, duration of Diabetes, and the presence of complications of Diabetes.

The Fremantle Diabetes Study assessed thyroid function for a group of 438females with Diabetes type 2coming under an observational study. Thyroid function tests, including thyroperoxidase antibodies, were measured

along with other parameters like HbA1C and lipid profile at baseline and after 5 years[61]. Exclusion criteria included Patients who previously had some form of thyroid dysfunction or is undergoing treatment for the same. The prevalence of SCHT was found to be 8.7%, and this prevalence was associated with an elevation in the antibodies to thyroid peroxidase, and age. However, the study could not associate Subclinical Hypothyroidism with the glycemic profile and lipid profile. Another fact that was observed was the patients who had Subclinical Hypothyroidism did not require any treatment and did not progress to overt hypothyroid disease after 5 years of follow up. Therefore, the screening of such patients for Subclinical Hypothyroidism remains questionable.

One of the most popular studies in thyroid disorders and Diabetes was performed in Greece in 2010, where a total of 1092 type 2 Diabetes mellitus were enrolled. About 12.3% of diabetic patients had thyroid dysfunction, out of which 80% were females. Other statistically significant parameters included a higher body mass index, a lower HDL cholesterol and a higher LDL cholesterol in patients with both thyroid dysfunction and hyperglycemia, compared to those with only hyperglycemia without thyroid dysfunction. There was no correlation between presence of thyroid dysfunction and Duration of Diabetes, blood pressure, glycemic control

(HbA1C), triglyceride levels, hypertension, and complications of Diabetes like retinopathy, nephropathy, and coronary artery disease.

There are very few studies that have compared the incidence of SCHT in the Indian subcontinent. The most significant was one trial performed in Bangladesh, who gathered one hundred and twenty individuals aged 41 – 70 years in Dhaka[62]. However, in the trial the incidence was very low, with only 2 individuals (3.33 percent) in the type 2 Diabetes group having Subclinical Hypothyroidism. Another case control study was performed by Sekar et al in North India, consisting of hundred cases and fifty controls, found the incidence of SCHT in type 2 Diabetes as 9 percent.

OTHER COMORBID CONDITIONS IN DIABETES

The Medical Expenditure Panel Survey is a group of surveys conducted on a large scale basis in families and employers in the United States. According to this survey, it is estimated that most adults suffer from one chronic comorbid condition (CCC) at the least, and around 40% individuals with Diabetes have three CCCs. These patients are defined patients with multimorbidity disease. The reason behind this is partly because of the improved quality in therapeutics and care provided to a diabetic, most notably improvements in HbA1C monitoring and glycaemic control. Cardiovascular deaths are in the decline because of more efficient use of medications like aspirin and angiotensin converting enzyme inhibitors. Due

to the extended longevity of diabetics, they are naturally more prone for more CCCs. Another important factor is the reduced patient provider visit time in the current era, considering the overwhelming number of health maintenance activities recommended by quality monitoring agencies, thereby leading to an inadequacy in health system support and a reduced experience in management of multimorbid patients by health care providers.

Moreover, the patients' ability in self-care management are profoundly affected by these comorbidities. As an example, depression and arthritis impairs the proper functioning of a patient and poses an enormous barrier to adherence to the prescribed regimen and changes in lifestyle. Certain CCCs can have a devastating effect on the patient's health status rather than the patient's diabetic status per se. Conditions like advanced heart failure make the attainment of the goals of Diabetes a Herculean task.

Chronic comorbid conditions increase the financial burden of an individual in terms of medications, investigations, and inpatient expenditure.

The following are the definitions for chronic comorbid conditions

Clinically Dominant conditions

Chronic comorbid conditions that are so serous / complex they mask the long term and short term management of other health problems.

- Recently diagnosed
    - Rheumatoid arthritis
    - Breast Cancer
- Severely symptomatic
    - Severe depression
    - Class IV chronic heart failure
- End-stage disease
    - Severe cognitive impairment or dementia
    - End stage renal disease

Asymptomatic versus symptomatic conditions

Treating of asymptomatic chronic conditions focus on prevention of early mortality and downstream adverse event exclusively

Treatment of symptomatic chronic conditions will be focused over delaying or preventing poor long term outcomes, and improving functioning and quality of life, and the patient's symptom profile.

- Asymptomatic
    - Hypertension
    - Moderate to poor glycaemic control
    - Hyperlipidemia

- Symptomatic
    - Depression
    - Angina
    - Gastroesophageal reflux disease
    - Rheumatoid arthritis

Discordant versus concordant conditions

Discordant conditions are those that are not related to Diabetes, in terms of management as well as in pathogenesis. Concordant conditions are more likely to be part of the spectrum of disease with the same overall pathophysiology and risk profile with probable improvement with treatment plan of the original disease.

- Discordance with diabetes
    - Chronic low backpain
    - Asthma
    - Prostatecancer
- Concordant with Diabetes
    - Coronary artery disease
    - Cerebrovascular disease
    - Hypertension.
    - Peripheral vascular disease.

Some conditions, even though vigilant Diabetes care is an essential part of management, are considered dominant by the health care providers. In a study of patients who are seropositive for human immunodeficiency virus (HIV), it was found that, the predominant reason for admission into the hospital was for exclusively non-HIV related conditions (72%). In such patients, where both diabetes and the seropositive status are health hazards, some physicians may place HIV above Diabetes as the dominant disease.

DIABETIC DYSLIPIDEMIA

Majority of the patients with type 2 Diabetes have some alteration in their lipid profile at some point in their life.The characteristic dyslipidemia pattern that accompanies hyperinsulinemia and insulin resistance is an elevation in the serum triglyceride levels and a reduction in the HDL - cholesterol levels, popularly known as diabetic dyslipidemia.The abnormalities in the lipid levels correlates with the insulin resistance severity. One trial detected insulin sensitivity using a euglycemic clamp in patients with and without type 2 Diabetes Mellitus found that there was an association between larger VLDL cholesterol particle size, smaller LDL cholesterol and HDL cholesterol and the resistance of peripheral tissues to insulin. There was also an increase in the concentrations of IDL, LDL and VLDL cholesterol with a consequent decrease in the concentrations of HDL cholesterol in these patients.

Kinetic studies in vitro have proved that there is a uniformly increased rate of secretion of VLDL, the major triglyceride-rich lipoprotein, in patients with type 2 Diabetes mellitus and hyperinsulinemia[48]. It has been shown in studies that lipoproteins that contain apoprotein B in their core are assembled and secreted in higher amounts after an increase in the influx of fatty acids into the liver in individuals with resistance to insulin. Increased secretion of apoprotein B containing lipoproteins also stimulates secretion of VLDL particles into the blood. VLDL, under the influence of cholesteryl ester transferring protein, then increases the rate of exchange of its triglycerides with cholesteryl ester that is present in HDL cholesterol, leading to the generation of HDL cholesterol particles that are rich in triglycerides. This TG-rich HDL acts as a substrate for the lipases either in the liver or in the capillary endothelium. The resultant smaller particles that are obtained after HDL triglyceride hydrolyzation will affect binding of ApooA1 to HDL. Using these assumptions, the conclusion of this study was that abnormalities in the lipid profiles in these individuals are mainly due to an increase in the transport of fatty acid into blood.

Therefore, two factors contribute to an increase in the triglyceride levels – 1) a decrease in the lipolysis of TG in VLDL cholesterol, and 2) an increase in the substrates available for lipoprotein metabolism, namely free fatty acids and glucose. For counteracting these disturbances Nicotinic acid is

a good therapeutic option, although the correction is only partial, and the fact that it is a double edged sword as it can increase the resistance to insulin and lead to a worsening of hyperglycemia has led to a reduction in its usage and popularity. For example, administering this drug in one of the trials led to a rise in haemoglobin A1C by 22%.

The prevalence for elevated LDL cholesterol was found to be similar in diabetic and non-diabetic patients of the Framingham study. This observation was further substantiated by the United Kingdom Prospective Diabetes Study (UK.PDS) where the levels of total cholesterol in diabetics wasn't varying compared to non-Diabetes, and LDL cholesterol level were more elevated in females but comparable in males of Diabetes type 2 on comparing with individuals without type 2 Diabetes. In spite of this similar prevalence of the level of cholesterol, individuals with type 2 diabetes are more prone for atherosclerotic injury. This is the result of altered glycosylation and oxidation of LDL particles in Diabetes. Therefore, even in patients who attain a level of LDL cholesterol below 50 mg/dL on non HDL cholesterol below 80 mg/dL, they have a persistent residual cardiovascular disease risk due to the significantly increased LDL particle number.

This altered lipid profile in diabetic patients pose an increased risk for cardiovascular morbidity and mortality. In a double blind, randomised five year trial, 4082 males with non HDL cholesterol more than 199 mg/dL were

subjected to gemfibrozil therapy aimed at raising HDL cholesterol as well as lowering non-HDL cholesterol[49]. The reduction in cardiac events incidence was 34% in the second year of the study itself. However, there was no difference in the mortality rates in the two groups.

In India, a prospective cross-sectional study was performed in a tertiary hospital in Gujarat[43]. Around 170 diabetics were enrolled in the study over a period of 6 months. The mean serum total cholesterol level was 190 mg/dL. Around 82.5% diabetic patients had dyslipidemia, most of them having a mixed pattern, and the prevalence was equally distributed among the urban as well as the rural population. The most common mixed pattern seen was a high LDL cholesterol with a high triglyceride level. During the enrolment period, most of them had an uncontrolled glycaemic profile, and the prevalence of dyslipidemia in the well-treated Diabetes group was significantly lesser. This showed that adequate glycemic control will eventually lead to returning of the lipid levels to normalcy. The prevalence of hypertriglyceridemia and high serum LDL (56 and 57% respectively) was much higher than that of low serum HDL cholesterol levels (35.7%). This study suggested that, instead of concentrating on a specific pattern of lipid abnormality in diabetic patients, it is better to screen the patient with a complete lipid profile as any combination of dyslipidemia may be seen in diabetics of the Indian population. Another study was done in south India on

820 patients with type 2 Diabetes, and dyslipidemia was prevalent in 95% males and 86% females. This study had a discrepancy in the pattern of dyslipidemia between the genders. While the male population had a predominant high triglycerides and low HDL cholesterol level, characteristic of dyslipidemia of Diabetes as mentioned in other studies, the female population had a higher prevalence of an elevated LDL cholesterol and low HDL cholesterol.

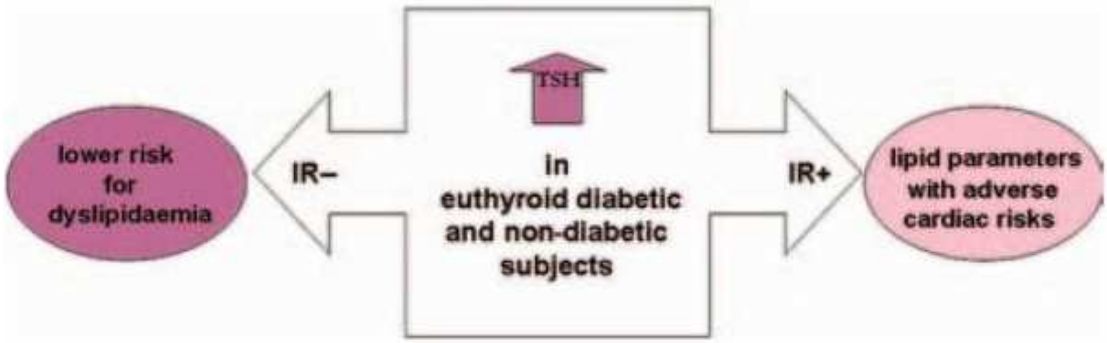
DYSLIPIDEMIA IN HYPOTHYROIDISM

The reason for an increased cholesterol level in thyroid hormone deficiency is primarily an increased LDL cholesterol accumulation because of a reduced number of LDL receptors on the surfaces of cells, thereby leading to a reduction in LDL catabolism. Another possible mechanism is a functional reduction in the LDL receptors, leading to an intrinsic resistance.

Upregulation of the LDL receptor by T4 therapy varies considerably in patients with different polymorphisms of the LDL receptor gene. In one study, patients homozygous for one specific genotype (-/-) had a four-fold greater reduction in serum cholesterol during T4 therapy than those who were homozygous for a different genotype (+/+).

There are other mechanisms that effect the level of cholesterol in the plasma in patients with documented thyroid hormone deficiency and these include:

1. A significant increase in oxidation of LDL particles, the rate of increase is proportional to concentration of serum LDL-C.
2. Decrease in the secretion of cholesterol to bile.
3. Reduction in transfer of cholesteryl ester in thyroid hormone deficiency will reduce the elevation in serum LDL cholesterol concentrations.



A reduction in the action of the capillary endothelial lipase (lipoprotein lipase) is the chief metabolic pathway for increased triglycerides in thyroid hormone deficiency.In two comparable studies, the level of triglycerides was increased in one study but normal in the other.

Chylomicron remnants accumulate in Hypothyroidism and are cleared more rapidly during T4 treatment.

Majority of individuals with SCHT havenormal values of serum total cholesterol and its fractions.Only a few studies have documented elevated levels of serum lipoprotein (a), triglycerides, total and LDL-cholesterol concentrations. The effects of thyroxine (T4) treatment on patients with SCHT were similar in three randomized studiesand two reviews of the literature: a mean reduction in serum total cholesterol of 10 to 16 mg/dL and in LDL cholesterolof 12 mg/dL. Effects of T4 may be more pronounced in those with overt hypercholesterolemia; in one study, as an example, serum LDL-cholesterol fell by 36 mg/dL (0.9 mmol/L, $p<0.01$) in such patients.The net effect of treating with T4 replacement on serum lipoprotein (a) levels in these individualsvary; in two studies, they declined by as much as 24 percent, but did not change in another study.

Serum HDL-cholesterol concentrations are low to normal in individuals with SCHT. The response to T4 therapy has been variable, but in the meta-analysis the serum HDL cholesterol concentration did not increase significantly.

Remnant lipoprotein concentrations (intermediate density lipoproteins), a predictor of coronary heart disease risk, may also be elevated in both overt and Subclinical Hypothyroidism with a lowering in response to T4 therapy.

Coronary heart disease may be increased among patients with Subclinical Hypothyroidism who have thyrotropin (TSH) values greater than 7 to 10 mIU/L.

In the Indian subcontinent, a case control study was done in Nepal on 80 patients, and it was seen that the cases had a significantly higher levels of total cholesterol, LDL cholesterol and triglycerides with an insignificant change in HDL and VLDL cholesterol compared to controls.

Singh K and colleagues performed a case control study on 100 cases of Subclinical Hypothyroidism. There was a significant increase in triglycerides and VLDL cholesterol levels compared to controls with almost similar abnormalities in LDL and HDL cholesterol levels[51]. Bandyopadhyay *et al* studied 100 patients with Subclinical Hypothyroidism aging 17-68 years and observed a significant elevation in total cholesterol, LDL cholesterol, and triglycerides, although this elevation was marked in the female population. In the male population there was a significant elevation only in the serum lipoprotein (a) levels[52]. Arsanna et al also conducted a case control study in Indian population with an aim to assess the association of lipid profile with Subclinical Hypothyroidism, and observed an elevated total and LDL cholesterol but no significant elevations in HDL cholesterol, triglycerides and VLDL cholesterol in the cases[53]. All these studies conducted in the Indian

population show an inconsistent pattern in the lipid profile in patients with Subclinical Hypothyroidism.

HYPOTHYROIDISM AND GLYCAEMIC PROFILE

Thyroid hormones have both promoting and inhibitory effects on glucose metabolism. An increased thyroid hormone level causes an increase in absorption of glucose from the gut, as occurs in hyperthyroidism. There is a resultant rise in plasma glucose level, but studies show that this rise is transient and causes an increase only in post prandial glucose levels. However, hyperthyroidism still promotes hyperglycemia, as there is an increased rate of degradation of insulin, which would lead to a decrease in its half-life. Bech et al noticed an increase in the levels of pro-insulin after a meal in untreated patients of Grave's disease. Another mechanism is an increased level of GLUT 2 receptors in the liver causing an increased hepatic glucose output in hyperthyroid patients.

In the hypothyroid patient, the increased weight gain and increase in the adipose tissue mass causes an elevation in insulin resistance and therefore a reduction in the peripheral utilization of tissues. This causes a rise in plasma glucose levels. However there is a compensatory decrease in the hepatic glucose output and so the hyperglycemia that occurs in hypothyroid patients does not appear to be significant.

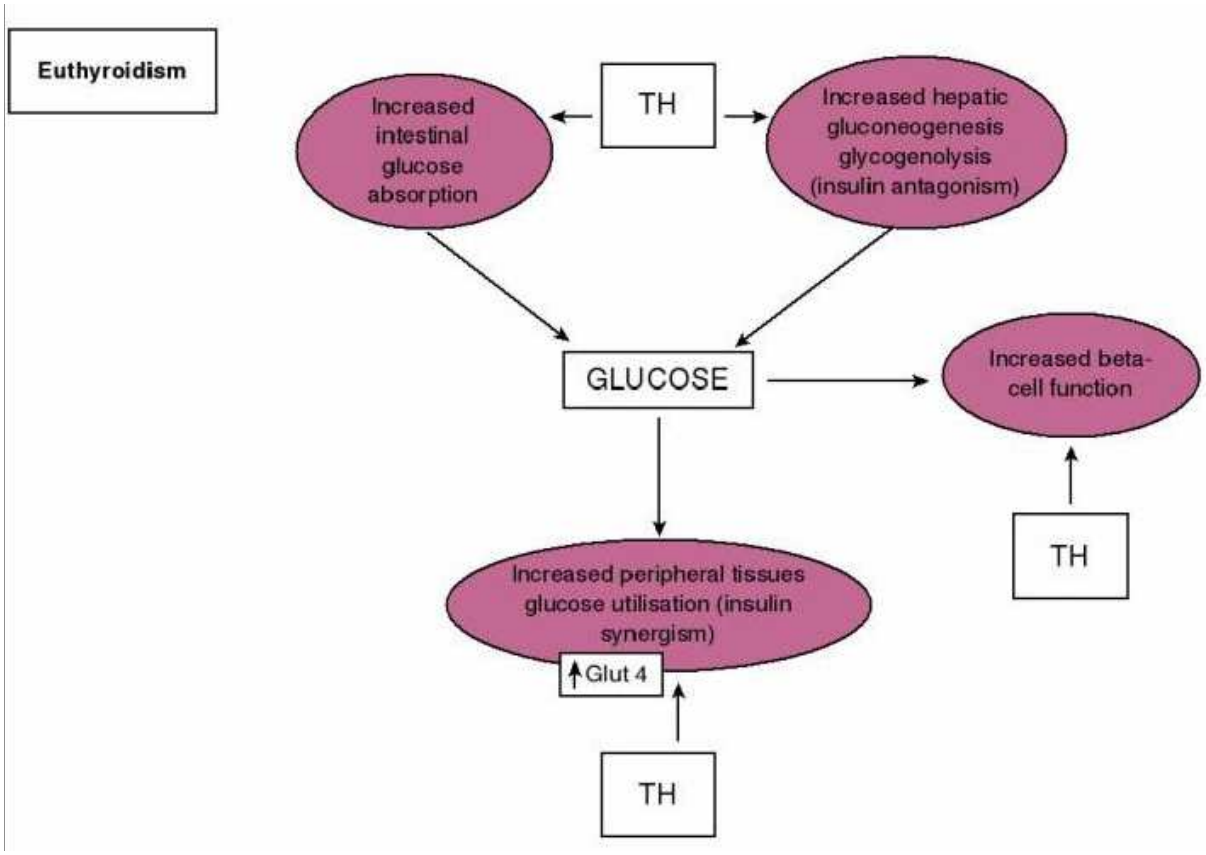
The cells used in metabolic studies of thyroid hormones are the monocytes as these cells contain receptors for insulin that quickly respond to any rise and fall of insulin concentrations, and, during the presence of insulin, they have a rapid rate of disposal of glucose. Monocytes also express the glucose transporter GLUT that is usually found in adipose and muscle tissue. In one study, it was observed that there was an impairment in the translocation of GLUT 4 transporters on cell membrane[54]. Another possible pathogenic mechanism causing hyperglycemia in Hypothyroidism is due to a reduced blood flow in peripheral tissues. It is known that T3 and insulin have similar sites of action for maintaining glucose homeostasis, and both have a synergistic action at both molecular and cellular levels in this aspect. Therefore, another possible hypothesis for an increased insulin resistance would be that a reduction in intracellular T3 could cause an impaired glucose uptake stimulated by insulin.

In one study, the level of insulin resistance was found to be the same in both overt as well as Subclinical Hypothyroidism[55]. This study questioned the possibility of a direct causation between the levels of thyroid hormones and hyperinsulinemia. However due to a higher level of insulin resistance even in subclinical cases of Hypothyroidism, this study warranted that a screening test must be applied to the general population to detect thyroid hormone abnormalities.

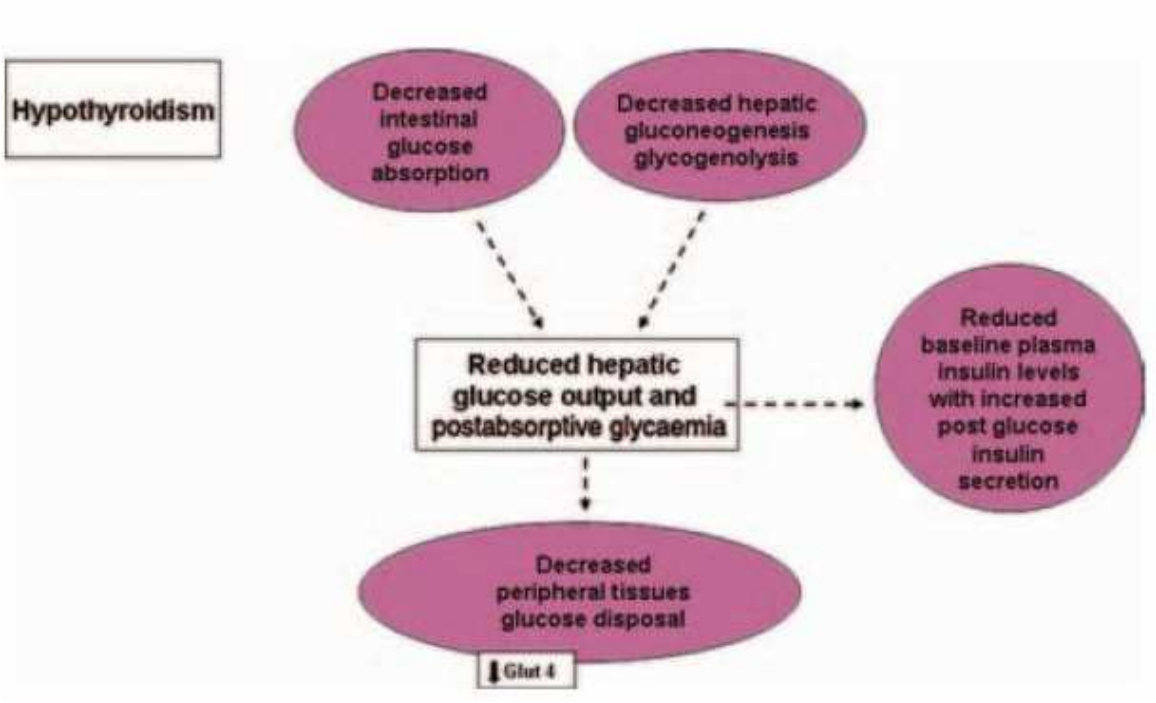
A study in India used Homeostatic model assessment (HOMA) to assess insulin resistance[56]. HOMA is a tool to determine insulin resistance and function of beta cells from C-peptide or insulin concentrations and a fasting glucose level, creating a mathematical model from which estimates of insulin sensitivity can be derived. The study was conducted on 25 female individuals aged 18 to 45 years each suffering from either Subclinical Hypothyroidism or overt Hypothyroidism without any previous known diseases like Diabetes, tuberculosis, liver disorders, congestive cardiac failure, medications that alter thyroid functions, polycystic ovarian disease, other systemic illnesses, chronic kidney disease, oral contraceptive or statin usage, who visited a tertiary care hospital in New Delhi. Pregnant females were also excluded from the study. Three groups of 25 each were formed – 'subclinical hypothyroid', 'controls' and 'overt hypothyroid' based on thyroid function tests. The HOMA IR in the control group was 0.57 (mean) as compared to 1.7 and 3.9 in subclinical and overt Hypothyroidism groups respectively. A significant correlation between insulin resistance and the TSH level in the overt Hypothyroidism group was noted.

Thyroid hormones may also have an influence on the metabolism of carbohydrates via adipokines and gut hormones. Thyroid hormone and adiponectin have certain similarities in properties like increased lipolysis and heat production[58]. Adiponectin interacts with gC1q receptor in thyroid

mitochondria and this may have an influence in the production of thyroid hormones. Moreover, T3 has been demonstrated to have an inhibitory effect in the mRNA expression of adiponectin in the white adipose tissue in rats. The levels of adiponectin in Hypothyroidism remains controversial with some studies showing normal levels of adiponectin (Nagasaki et al in Tokyo, 2005) while others showing a decreased level in Hypothyroidism (Dimitriadis et al in Greece, 2006[59]). Another important adipokine is the hormone leptin. This hormone produced in the white adipose tissue regulates body weight and temperature. Controversial reports have been observed regarding its plasma levels in Hypothyroidism as well.



Hypothyroidism can also be on the other extreme, causing multiple hypoglycaemic attacks in a previously euthyroid patient. The decreased rate of hepatic glucose output production would also lead to a reduction in the requirement of insulin in the patient. Leong et al demonstrated this phenomenon in patients with Addison's disease and type 1 Diabetes and thyroid dysfunction – he also observed that after replacement therapy with thyroid hormones, the fluctuations in sugar levels decreased.



EFFECTS OF DIABETES MELLITUS ON THYROID HORMONE LEVELS

Thyroid disease has been documented in patients with Diabetes mellitus, more significantly in those with a poor glycaemic control. In diabetic patients, there occurs a blunting of the nocturnal TSH peak, so the

TSH response to an increased hypothalamic thyrotropin releasing hormone (TRH) is impaired, leading ultimately to a 'low T3 state'. This was partially explained by an impaired peripheral conversion of T4 to T3 in some studies. Consequently, an improvement in thyroid function is expected as glycaemic control is achieved, but this relation was not observed in a study by Coiro et al in type 1 Diabetes patients[60]. Hyperinsulinemia and insulin resistance is related to increased nodularity of the thyroid gland and a Grave's thyrotoxicosis can ensue. Also the retinopathy in Diabetes renders the retina and optic nerve more susceptible to damage, so in Grave's disease patients with Diabetes, a higher incidence of dysthyroid optic neuropathy has been observed.

CONSEQUENCES OF SUBCLINICAL HYPOTHYROIDISM IN DIABETES MELLITUS

Very few studies have been conducted in patients having both Subclinical Hypothyroidism and Diabetes mellitus, and the possible complications that could occur at a higher frequency in such individuals.

As a fact, both the diseases are risk factors for dyslipidemia, and so the lipid levels are naturally expected to have a more elevated level in these patients. But there are conflicting reports as to the pattern of dyslipidemia. Diabetes typically tends to increase the triglyceride level, and lower the HDL cholesterol level, whereas Hypothyroidism tends to increase the LDL

cholesterol and triglyceride levels. In a study in Greece on diabetic patients, those with thyroid disorders had a better lipid profile compared with those without thyroid disorders[57]. The reason given for this improvement is that the patients were on thyroid hormone replacement therapy with thyroxine, which would improve the lipid profile status.

Hypothyroidism may have an adverse outcome in relation to nephropathy, retinopathy and cardiovascular events in diabetic individuals. In a cross sectional study performed in Taipei, Taiwan, a greater prevalence of diabetic nephropathy, but not of diabetic retinopathy, was observed in type 2 Diabetes patient with a coexisting SCHT, and a risk of cardiac and vascular disease was significantly more in the group with coexisting SCHT. However, the all-cause mortality in the two groups did not significantly differ.A retrospective study in 1993 – 2005 taking into account 6540 diabetics found that in 472 patients who were diagnosed with a raised TSH, when compared to 472 age and sex matched diabetics with normal TSH level, the all-cause mortality was less in the group with Subclinical Hypothyroidism (24.4%) compared to the group without (32.8%). There was also no significant connection between TSH level and cardiovascular mortality. This study was against the fact that type 2 Diabetes patients with SCHT are at increased risk of adverse cardiovascular events.

TREATMENT OF HYPOTHYROIDISM

Treatment of hypothyroidism focuses mainly on hormone replacement therapy with levothyroxine. The usual dose of l-thyroxine used is 1.5microg/kg wt. per day, which usually amounts to 100 to 150 micrograms. However, low doses are sufficient for many patients till the destruction of residual thyroid tissue. In individuals who develop hypothyroidism after therapy for toxic nodular goitre, the thyroid gland develops an autonomous function, so doses of thyroxine replacement needs to be lowered to 70 to 120 micrograms.

Adults below sixty years without any previous history or current symptoms and signs of cardiac or vascular disease need to be started on fifty to hundred micrograms of l-thyroxine per day. Based on plasma thyrotropin (TSH) levels, the dose can be heightened or tapered, the aim of therapy being attainment of normal baseline TSH levels, preferably to the lower half of the normal limits. The response to hormone replacement therapy is gradual and repeat measurements of TSH should be done 2 months after starting therapy or after altering the dose. The clinical improvement after thyroxine therapy are even slower to occur. Full resolution of symptoms may not occur till three to six months even after TSH levels are normalized. L-thyroxine dose may need to be adjusted and this is done either by 12.5 or 25 microgram increase or decrease if TSH is elevated or low respectively. There is an elevated risk

of reduction in density of bone and atrial fibrillation in patients with a decreased TSH, whatever be the etiology, including excess therapy with T4.

The usage of liothyronine, the commercial preparation of the thyroid hormone T3 (triiodothyronine) has been tried along with l-thyroxine, but more trials are required to prove its beneficial effects. Liothyronine alone is not of any use, especially in management on a long term basis, since the small half-life makes three or four doses per day necessary, and it is also associated with fluctuation of T3 levels.

After achievement of replacement and stabilisation of TSH concentrations, annual follow-up is suggested by measuring plasma TSH levels, and if the patient is able to maintain his TSH at a normal limit for many years, the follow-up may be extended to once every two to three years. It is crucial to make sure that the patient is adherent to therapy because once the patient improves from symptoms and signs, he/she may think of discontinuing therapy without consulting a specialist.

If the dose of l-thyroxine exceeds 200 micrograms per day, elevation of the TSH concentration is a reliable marker of inadherence to therapy. This inadherence can also explain the fluctuation in the TSH concentrations, in spite of a stable l-thyroxine dose. Such individuals usually have a high to normal unbound T4 concentrations, in spite of a high TSH level. It is necessary to keep this in mind since such a pattern is also suggestive of

disorders of the pituitary gland (secondary thyroid disorders). If an individual misses a dose, he/she can take two doses at once the next day. This property is attributable to the long half-life of T4 (seven days).

Most guidelines suggest therapy for Subclinical Hypothyroidism only if the plasma TSH levels exceed 10 mU/L. Transient thyrotropin elevations must be kept in mind and only if TSH concentrations are high even after three months, it is advisable to begin therapy. Therapy for individuals with TSH concentrations below 10mU/L remains a controversy, but as long as overtreatment is prevented, correction of slightly elevated thyrotropin concentrations is harmless, it may even be beneficial. Therefore, therapy is usually begun with a low dose of replacement and then slowly increased to attain normalisation of TSH levels.

MATERIALS AND METHODS

MATERIAL AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, and Madras Medical College, Chennai.

ETHICAL COMMITTEE APPROVAL:

Obtained.

CONSENT:

Written informed consent obtained.

STUDY DURATION:

This study was conducted over a period of six months from March 2014 to August 2014.

STUDY POPULATION:

Patients attending the outpatient department of Internal Medicine and patients admitted under the Institute of Internal Medicine who satisfy the inclusion and exclusion criteria.

SAMPLE SIZE:

Two hundred Individuals

TYPE OF STUDY:

Observational study (Prospective cum Retrospective)

INCLUSION CRITERIA:

- Patients aged above 40 years with a past history of type 2 Diabetes mellitus

EXCLUSION CRITERIA:

- Patients not willing to give consent
- Patients below 40 years
- Patients with history of a known thyroid disease
- Patients with biochemical or clinical features of hyperthyroidism
- Patients with a critical illness like malignancy, heart failure
- Patients with abnormal liver or renal function

DATA COLLECTION AND METHODS:

Relevant history of the patient is taken as per the questionnaire and the patient is also subjected to clinical examination and diagnostic investigations. Informed as well as written consent was attained from either the eligible patients or their legal representatives. Cases were screened according to inclusion and exclusion criteria. All the cases and controls were subjected to clinical and laboratory investigations as per the proforma. The age, diabetic

status, medication history, past and family history, were obtained by self-report. Blood pressure measurements were made in the right upper limb in supine posture using a standardized digitals phygmomanometer. Patients were subjected to a complete General physical and systemic examination and special emphasis made to screen for the microvascular and macrovascular complications of Diabetes. A complete blood count, a liver function test, a renal function test, serum electrolyte panel, fasting lipid and glucose levels were all obtained using standard assays. The HbA1C levels were also obtained from the patients. Lipid profile included Total cholesterol, LDL cholesterol, HDL cholesterol and plasma triglycerides. Fasting thyroid profile including plasma free T3, free T4, and plasma TSH were obtained using standard assays. The data collected were entered in the proforma and subjected to statistical analysis.

STATISTICAL ANALYSIS:

Analysis was done using SPSS Version 20. Significance was assumed with p value of 0.05. Association between two categorical variables was tested using Chi square test. All p values were two tailed and significant when values were less than 0.05.Results of logistic regression were given ass Odds ratio with 95% Confidence Interval.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND ANALYSIS

TABLE 1 –PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM:

	Frequency	Percentage (%)
Normal	168	84
Subclinical Hypothyroidism	24	12
Overt Hypothyroidism	8	4
Total	200	100

P value 0.025

CHART 1 - PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

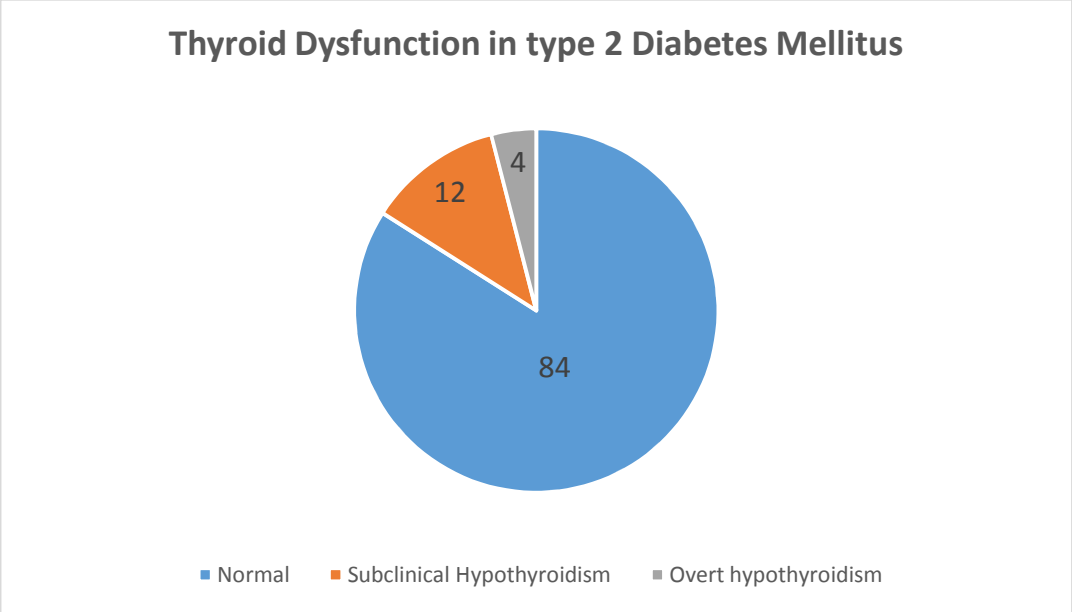


TABLE 2 –AGE DISTRIBUTION

Age	Normal		Subclinical Hypothyroidism		Overt Hypothyroidism		Total	
	No.	%	No.	%	No.	%	No.	%
40 – 45	29	90.6	3	9.4	0	0	32	100
46 – 55	74	88.1	6	7.1	4	4.8	84	100
56 – 65	34	68.0	13	26.0	3	6	50	100
66 – 75	25	89.3	2	7.1	1	3.6	28	100
>75	6	100	0	0	0	0	6	100
Total	168	84	24	12	8	4	200	

P value 0.450

CHART 2.1 – AGE DISTRIBUTION

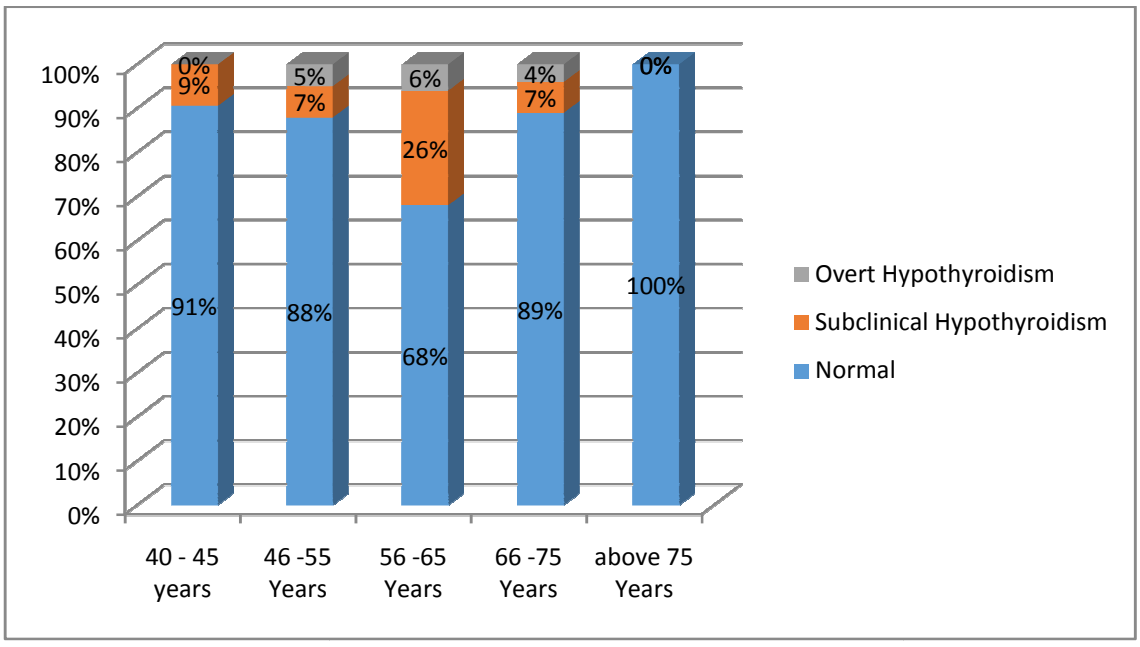


CHART 2.1 – AGE DISTRIBUTION OF PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

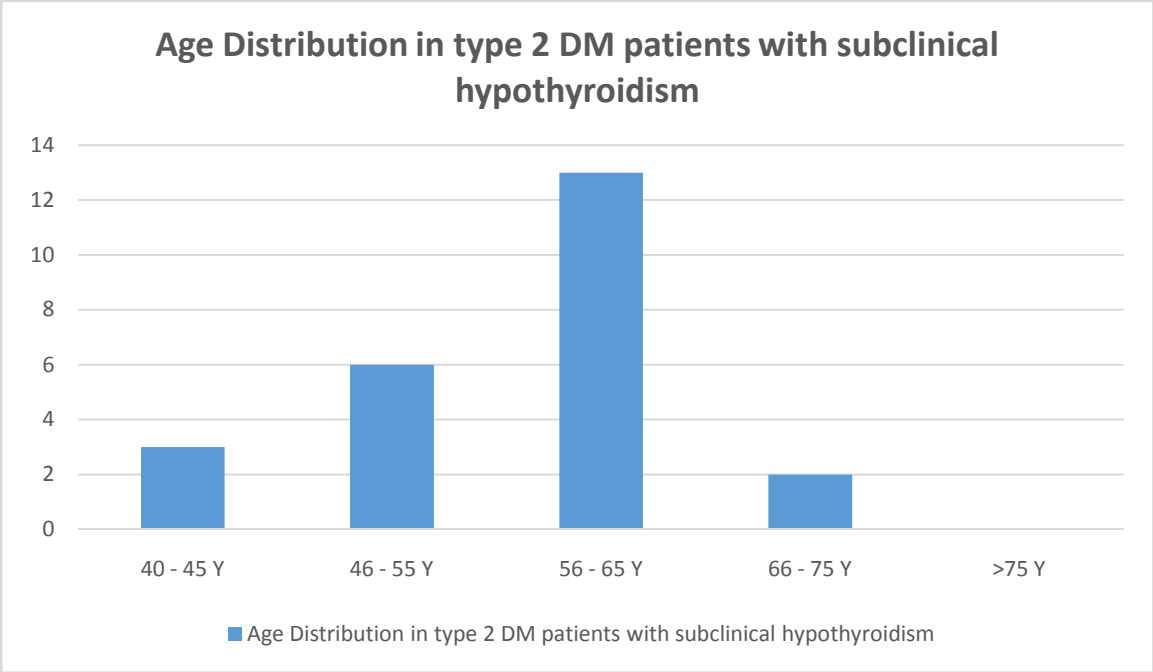


TABLE 3 - GENDER DISTRIBUTION

	Male	Female	Total
Normal	80 (87%)	88 (81.5%)	168 (84%)
Subclinical Hypothyroidism	9 (9.8%)	15 (13.9)	24 (12%)
Overt Hypothyroidism	3 (3.3%)	5 (4.6%)	8 (4%)
Total	92	108	200

P value 0.045

CHART 3.1 – GENDER DISTRIBUTION

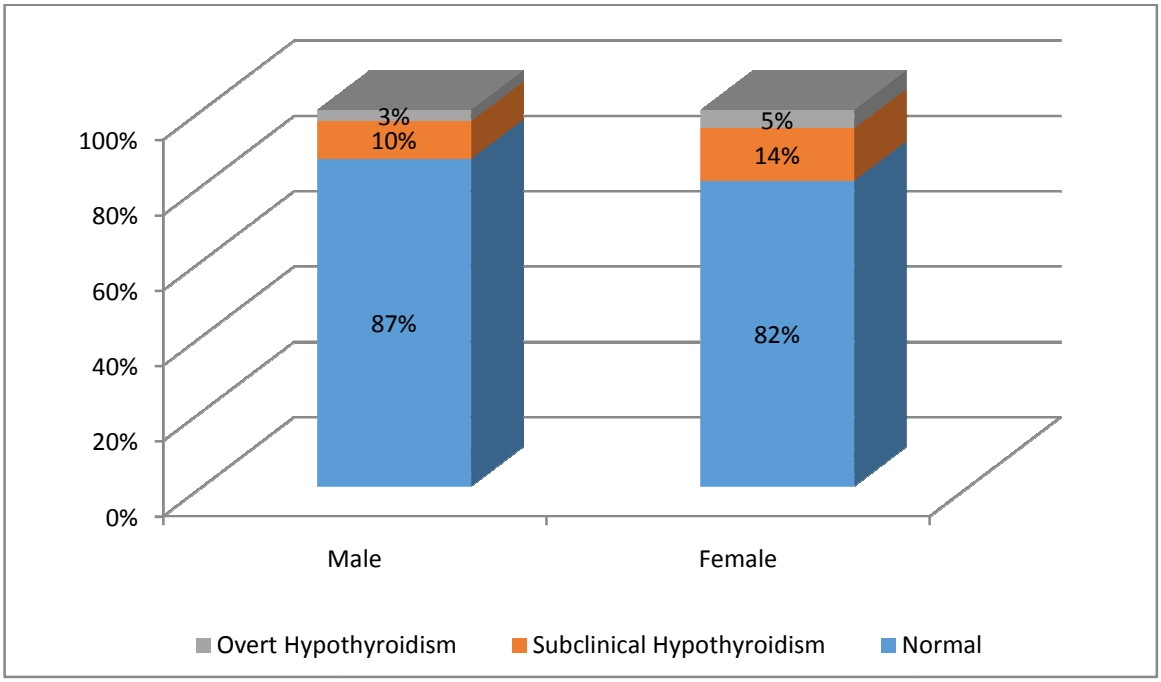


CHART 3.2 – GENDER WISE DISTRIBUTION OF PATIENTS WHO HAD SUBCLINICAL HYPOTHYROIDISM

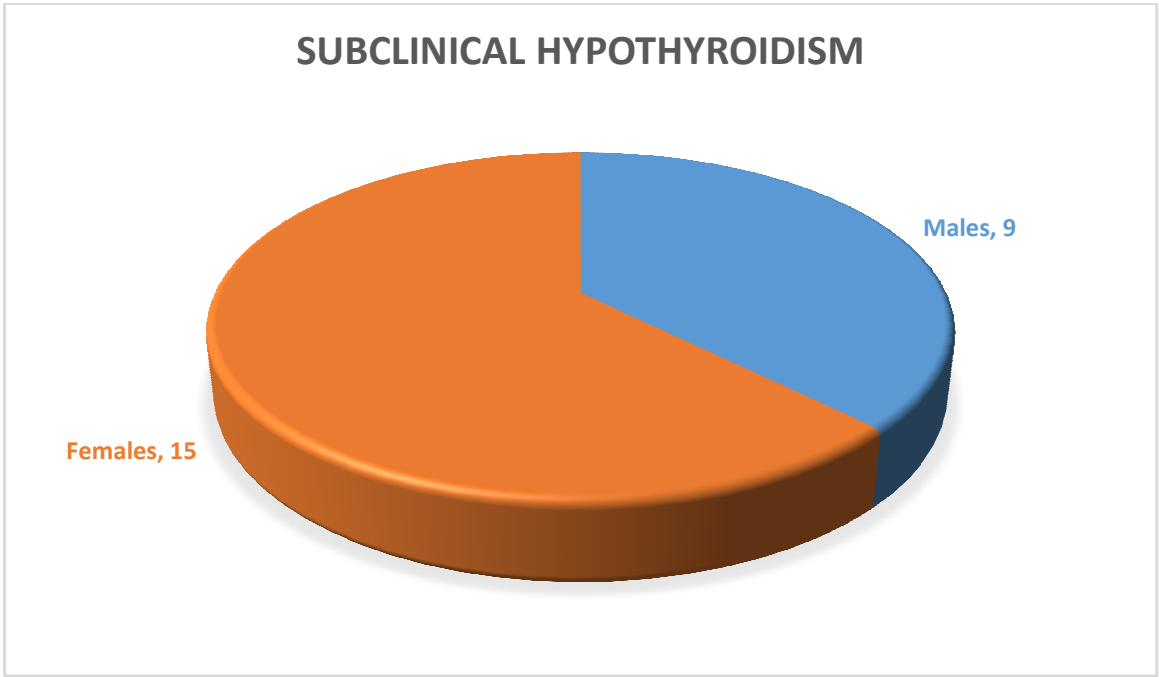


CHART 3.3 – GENDER DISTRIBUTION IN PATIENTS WHO HAD OVERT HYPOTHYROIDISM

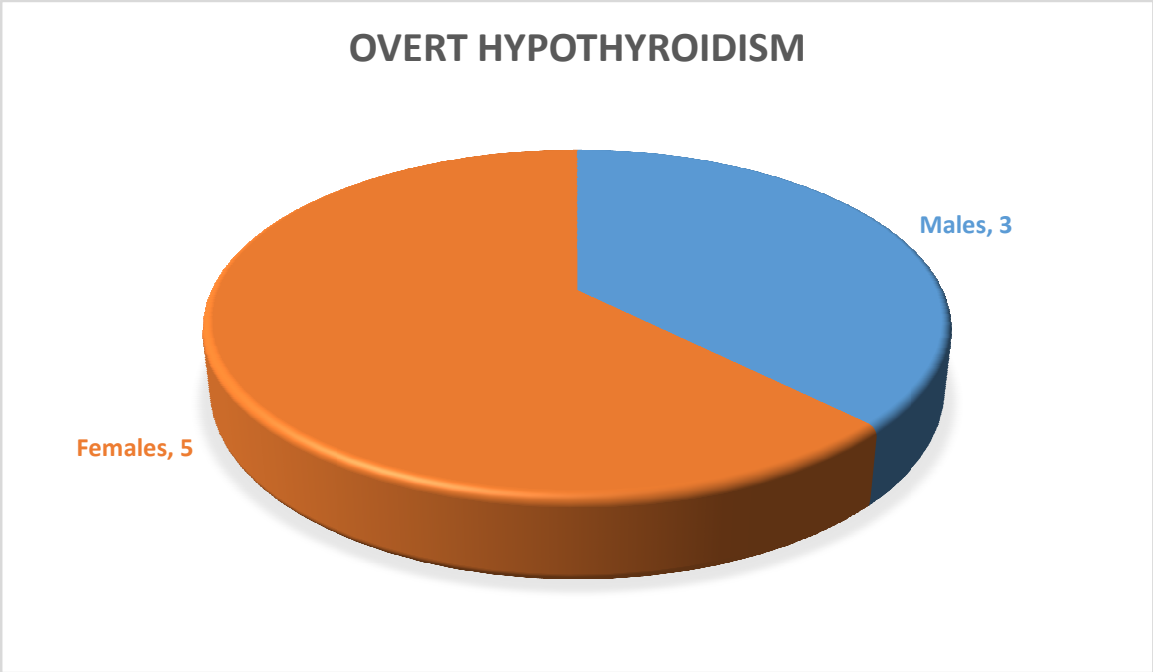


TABLE 4.1 – RELATION BETWEEN HbA1C AND TSH

TSH (microIU/mL)	TSH 0.3 – 5.5	TSH 5.5 – 6.5	TSH > 6.5	Total
HbA1C < 7%	56 (33.3%)	0 (0%)	3 (15%)	59
HbA1C 7 – 8%	51 (30.4)	6 (50%)	5 (25%)	62
HbA1C 8 – 9%	34 (20.2)	1 (8.3%)	1 (5%)	36
HbA1C 9 – 10%	9 (5.4)	1 (8.3%)	2 (10%)	12
HbA1C > 10%	18 (10.7)	4 (33.3%)	9 (45%)	31
	168	12	20	200

P value 0.25

CHART 4.1 – RELATION BETWEEN HbA1C AND TSH

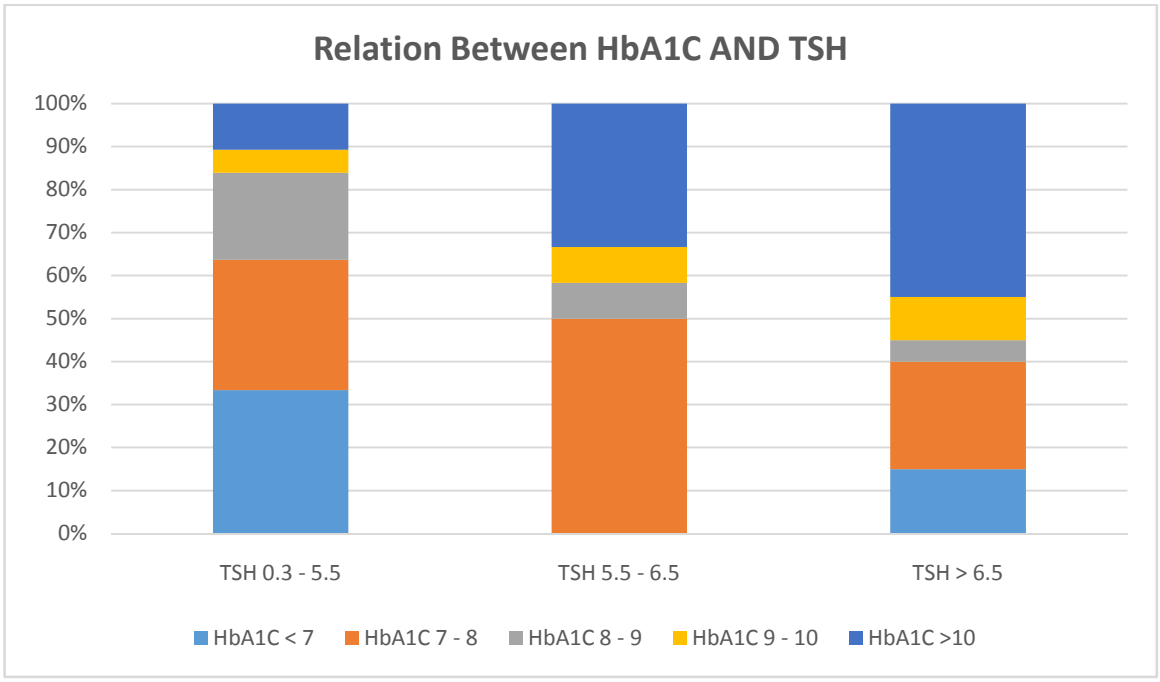


CHART 4.2 – RELATION BETWEEN HbA1C AND TSH

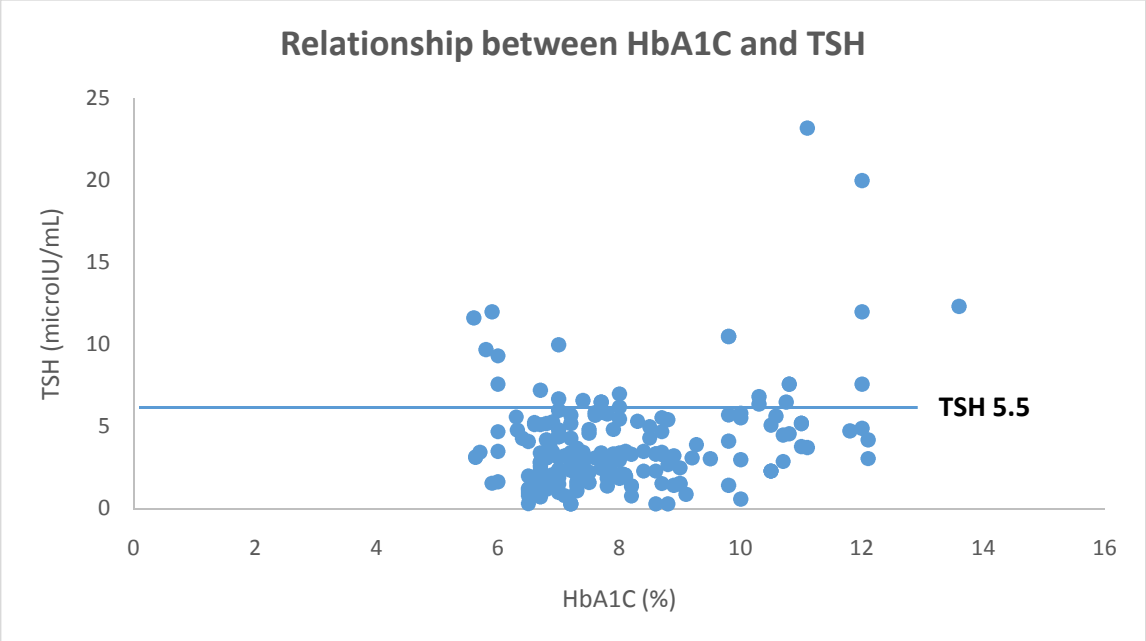


CHART 4.3 – HbA1C in SUBCLINICAL HYPOTHYROIDISM

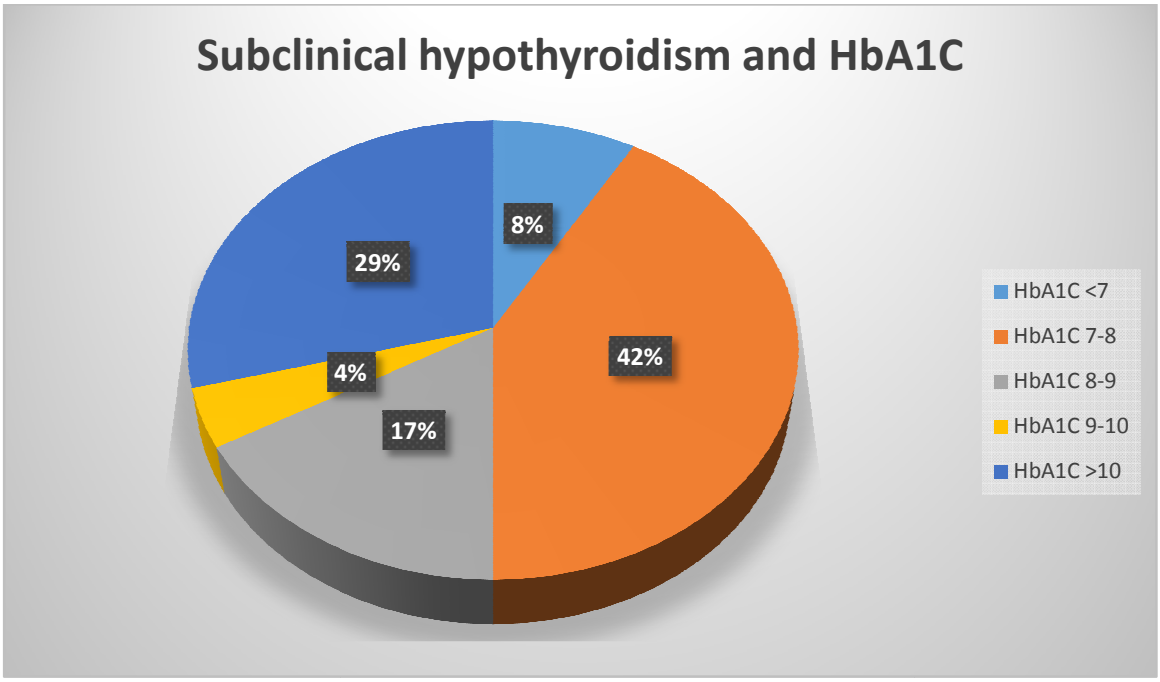


TABLE 4.2 – MEAN HbA1C IN TYPE 2 DM WITH AND WITHOUT HYPOTHYROIDISM

	N	Mean HbA1C	SD
Normal	168	7.9242	1.543
Subclinical Hypothyroidism	24	8.531	1.644

TABLE 5.1 – DURATION OF DIABETES AND TSH

TSH (mu/ml)→ Duration of Diabetes	0.3 – 5	5 – 5.5	5.5 – 6.5	>6.5	Total
<1 year	2 (1.2%)	0	2 (13.4)	0 (0)	2
1-4 years	42 (27.3%)	6(42.9%)	3 (20%)	4 (23.5%)	55
4-7 years	42 (27.3%)	3(21.4)	5 (33.3%)	4 (23.5%)	54
7-10 years	21 (13.6%)	1(7.1)	2 (13.3%)	6 (35.3%)	32
>10 years	47(30.6%)	4(28.5%)	3 (20%)	3 (17.6%)	57
Total	154(100%)	14(100%)	15 (100%)	17 (100%)	200

P = 0.450

CHART 5.1 – DURATION OF DIABETES AND TSH

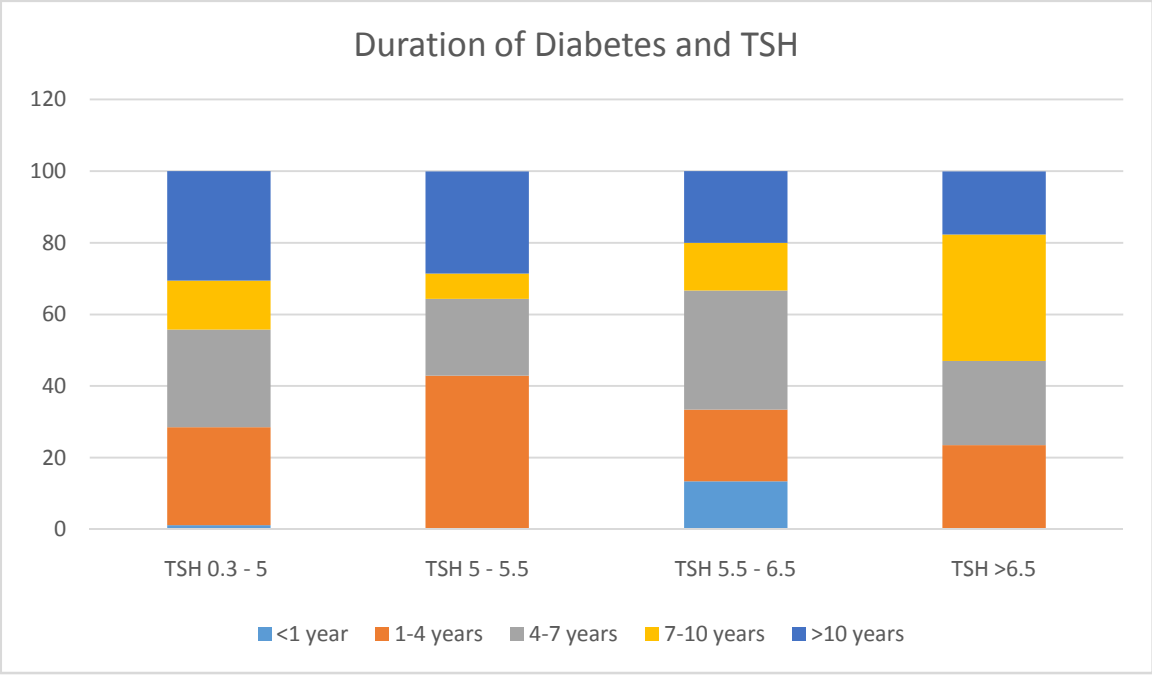


CHART 5.2 DURATION OF DIABETES IN SUBCLINICAL HYPOTHYROIDISM

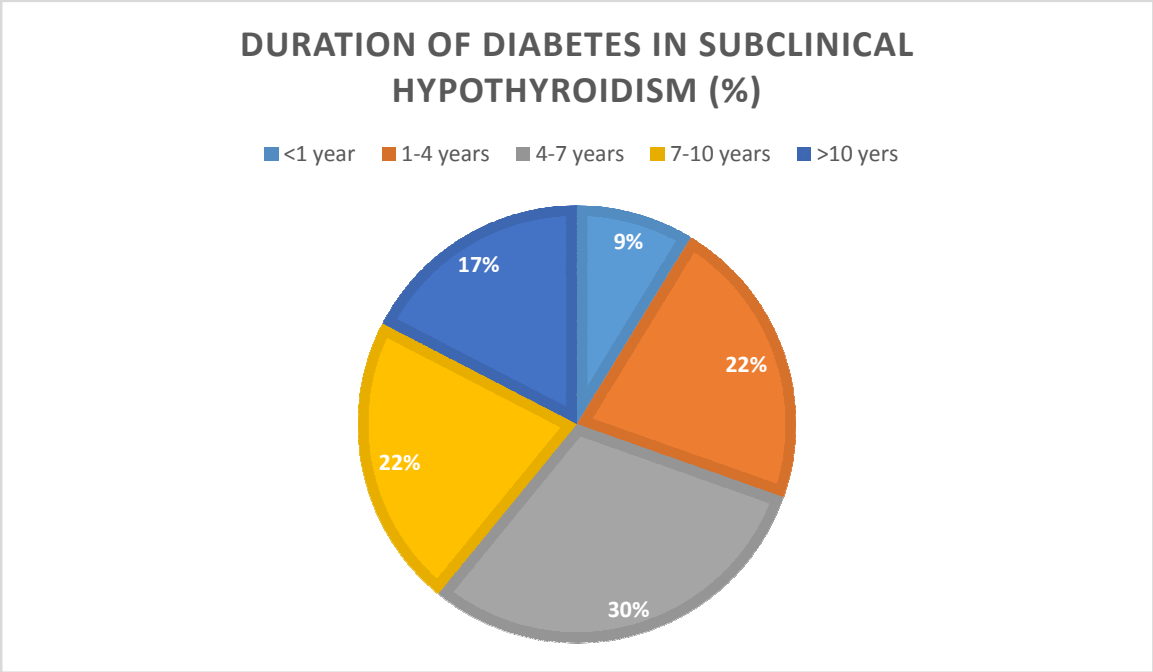


TABLE 5.2 – MEAN DURATION OF DIABETES IN T2DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

	N	Mean duration	SD
Normal	168	7.28 years	5.37
Subclinical Hypothyroidism	24	5.72 years	3.19

TABLE 6.1 – TOTAL CHOLESTEROL IN T2DM WITH AND WITHOUT THYROID DYSFUNCTION

Total Cholesterol	Normal	Subclinical Hypothyroidism	Overt Hypothyroidism	Total
<200 mg/dL	117 (69.6%)	13 (54.1%)	5 (62.5%)	135
>200 mg/dL	51 (30.4%)	11 (45.9%)	3 (37.5%)	65
Total	168 (110%)	24 (100%)	8 (100%)	200

P value 0.309

CHART 6.1 – TOTAL CHOLESTEROL IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM (%)

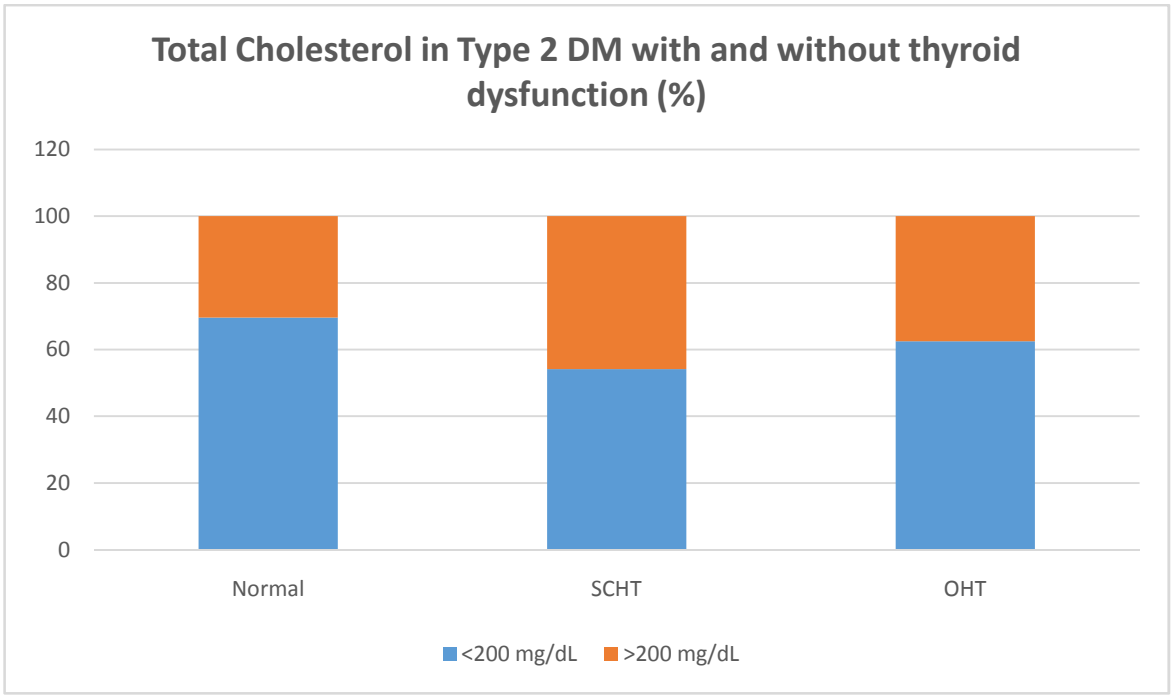


TABLE 6.2 – LDL CHOLESTEROL IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

LDL Cholesterol	Normal	Subclinical Hypothyroidism	Overt Hypothyroidism	Total
<100 mg/dL	79 (47%)	8 (33.3)	5 (62.5%)	95
>100 mg/dL	89 (53%)	16 (66.7)	3 (37.5%)	105
Total	168 (100%)	24 (100%)	8 (100%)	200

P value 0.094

CHART 6.2 - LDL CHOLESTEROL IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

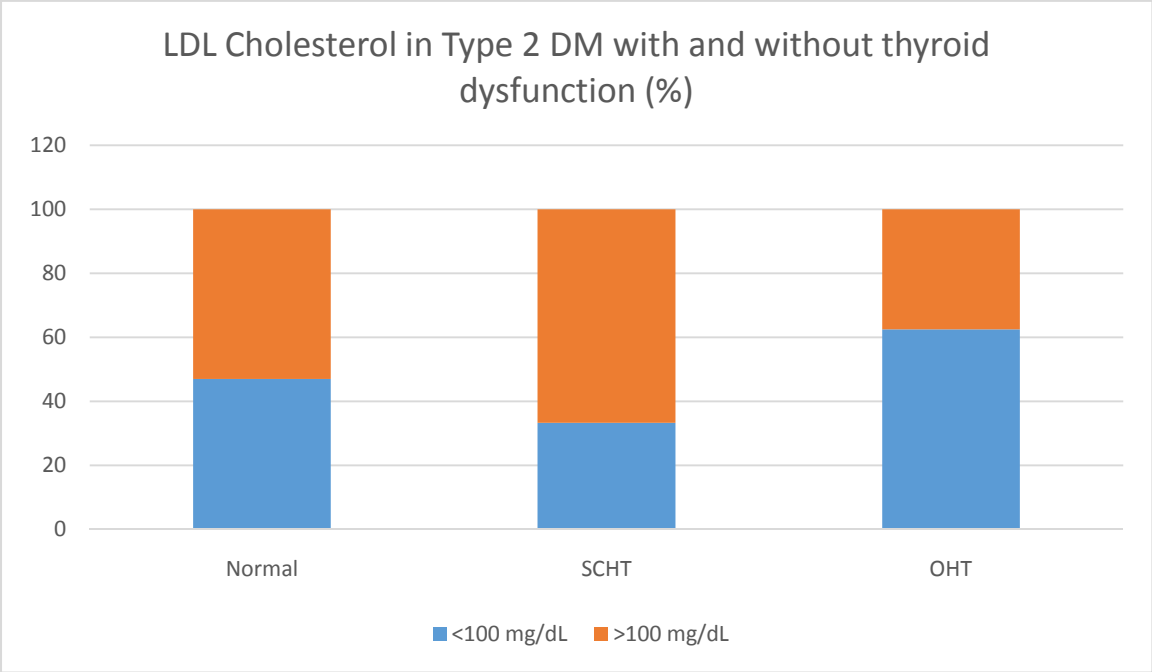


TABLE 6.3 – HDL CHOLESTEROL IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

HDL Cholesterol	Normal	Subclinical Hypothyroidism	Overt Hypothyroidism	Total
>40 mg/dL	102 (60.7%)	12 (50%)	3 (37.5%)	117
<40 mg/dL	66 (39.3%)	12 (50%)	5 (62.5%)	83
Total	168 (100%)	24 (100%)	8 (100%)	200

P value 0.632

CHART 6.3 – HDL CHOLESTEROL IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

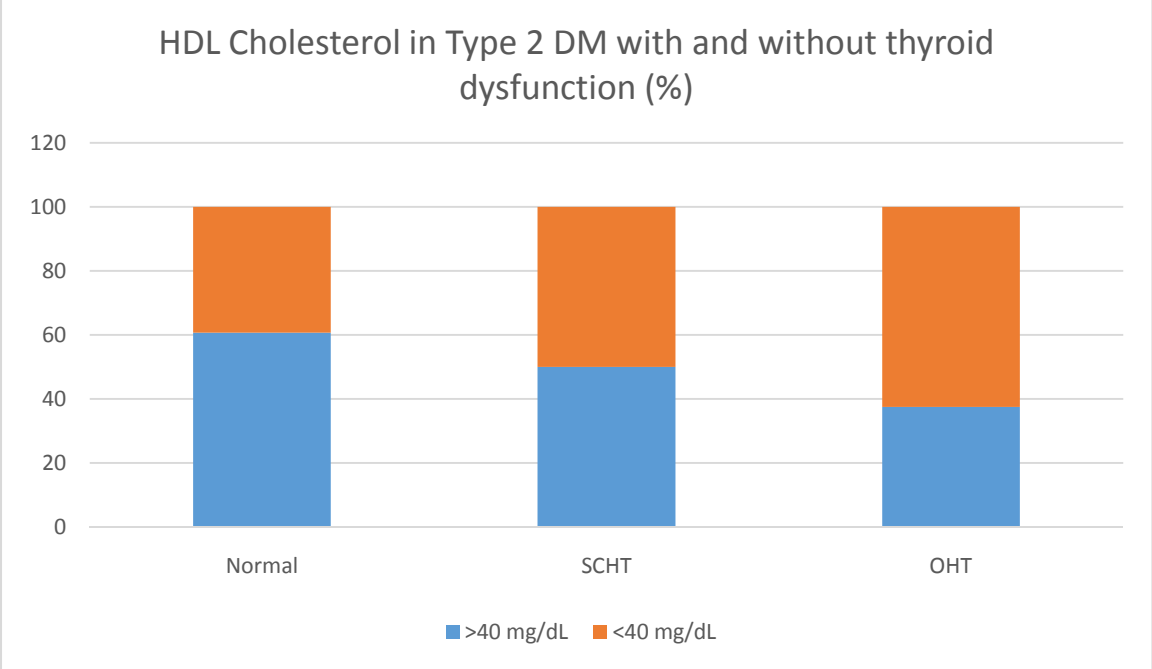


TABLE 6.4 – SERUM TRIGLYCERIDE LEVELS IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

Serum Triglycerides	Normal	Subclinical Hypothyroidism	Overt Hypothyroidism	Total
<100 mg/dL	79 (47%)	0 (0%)	2 (25%)	81
100 - 149 mg/dL	66 (39.3%)	5 (20.8%)	1 (12.5%)	72
>150 mg/dL	23 (13.7%)	19 (79.2)	5 (62.5)	47
Total	168 (100%)	24 (100%)	8 (100%)	200

P value 0.008

CHART 6.4 – SERUM TRIGLYCERIDE LEVELS IN TYPE 2 DM WITH AND WITHOUT SUBCLINICAL HYPOTHYROIDISM

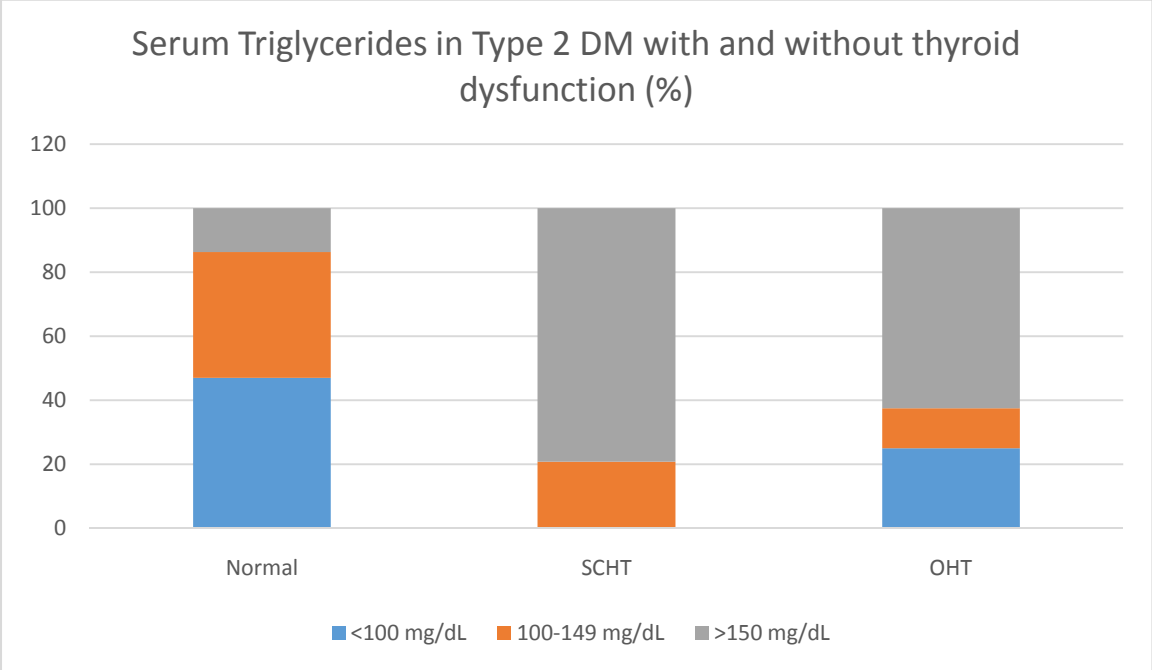


TABLE 6.5 – MEAN VALUES OF CHOLESTEROL LEVELS AND TRIGLYCERIDES IN TYPE 2 DM WITH AND WITHOUT THYROID DYSFUNCTION

	Total Cholesterol		LDL-C		HDL-C		Triglycerides	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Normal	181.9	36.16	108.39	33.9	42.44	7.5	151.3	45.17
Subclinical Hypothyroidism	189.17	35.5	121.15	34.1	42.45	12.1	184.4	44.8
Overt Hypothyroidism	193.2	37.3	108.9	30.7	39.3	10.6	148.3	35.1

CHART 6.5 – MEAN VALUES OF CHOLESTEROL LEVELS AND TRIGLYCERIDES IN TYPE 2 DIABETES MELLITUS WITH AND WITHOUT THYROID DYSFUNCTION

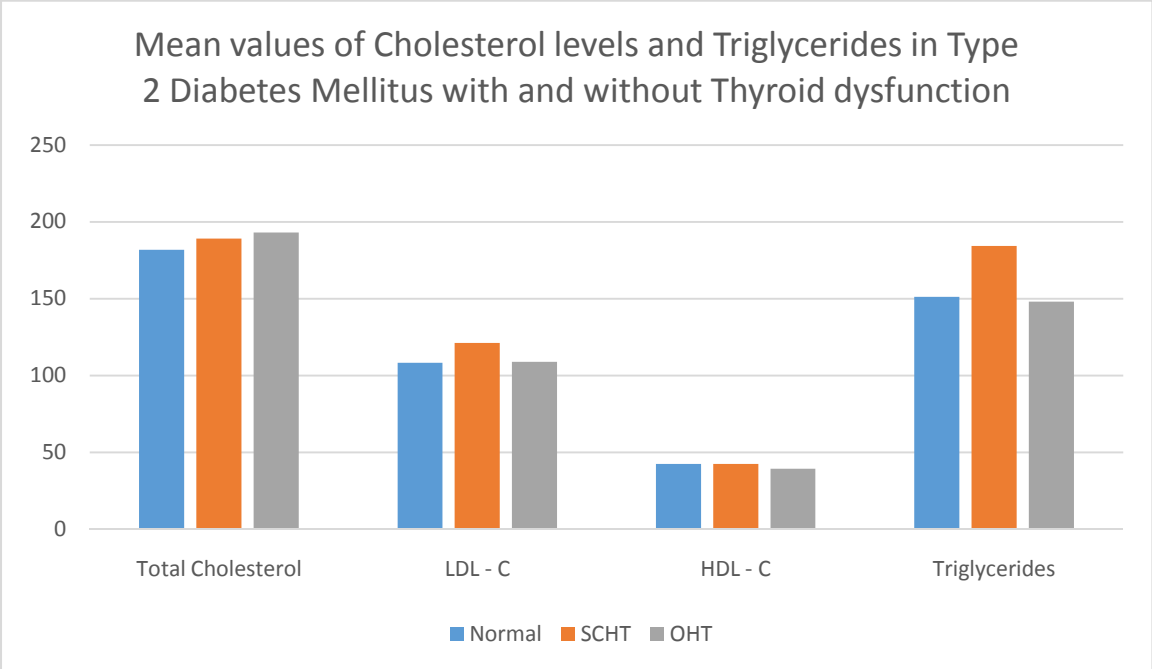


TABLE 7 – AGE AND GENDERWISE DISTRIBUTION OF SERUM TRIGLYCERIDE LEVELS IN TYPE 2 DM AND SUBCLINICAL HYPOTHYROIDISM

Triglycerides (mg/dL)	<50 years		50 – 70 years		>70 years		Total
	M	F	M	F	M	F	
<150	0	1	1	2	0	1	5
150 – 200	0	5	4	0	0	0	9
>200	0	1	4	5	0	0	10
Total	0 (0%)	7 (29.2%)	9 (37.5%)	7 (29.2%)	0 (0%)	1 (4.1%)	24

CHART 7 - AGE AND GENDERWISE DISTRIBUTION OF SERUM TRIGLYCERIDE LEVELS IN TYPE 2 DM AND SUBCLINICAL HYPOTHYROIDISM

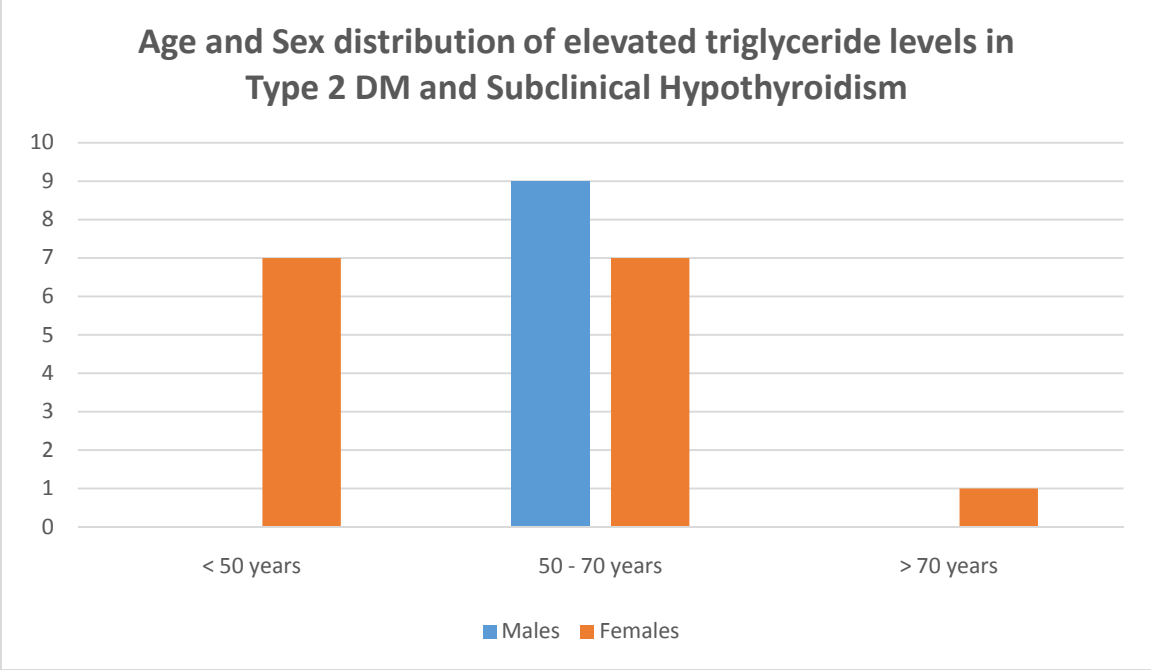


TABLE 8.1 – GENDER DISTRIBUTION OF TYPE 2 DIABETES PATIENTS WITH AND WITHOUT DYSLIPIDEMIA

	Normal lipid profile	Dyslipidemia	Total
Males	25 (27.2%)	67 (72.8%)	92 (100%)
Females	22 (20.4%)	86 (79.6%)	108 (100%)
Total	47	153	200

P value 0.924

CHART 8.1 - GENDER DISTRIBUTION OF TYPE 2 DIABETES PATIENTS WITH AND WITHOUT DYSLIPIDEMIA

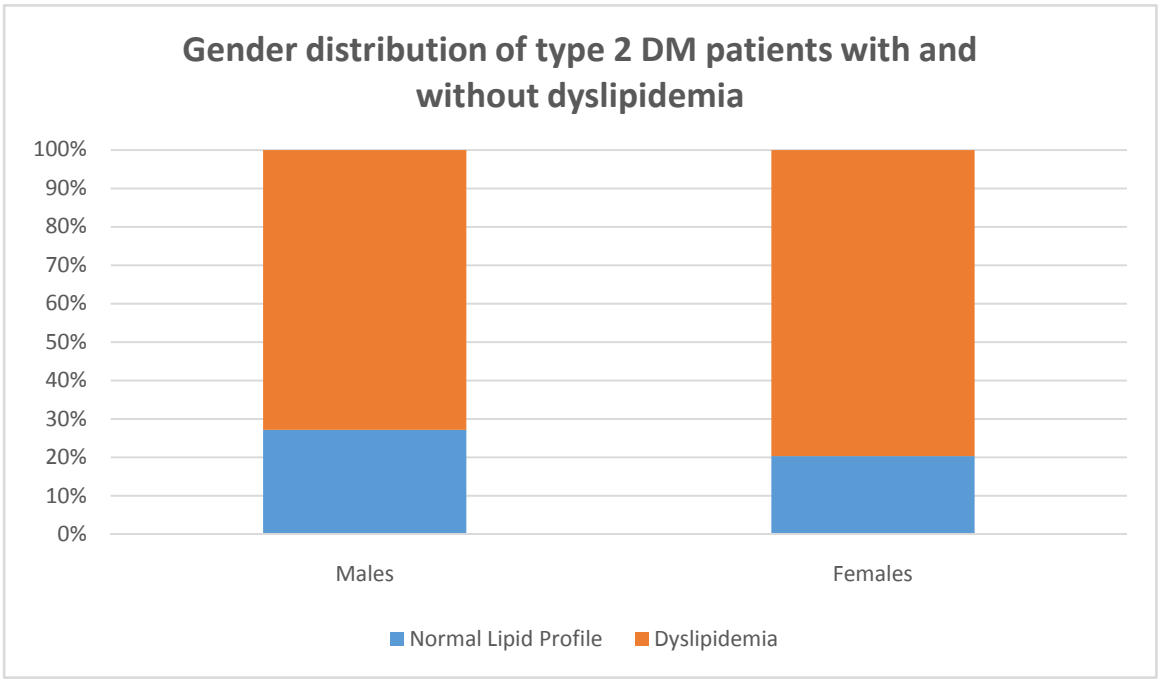
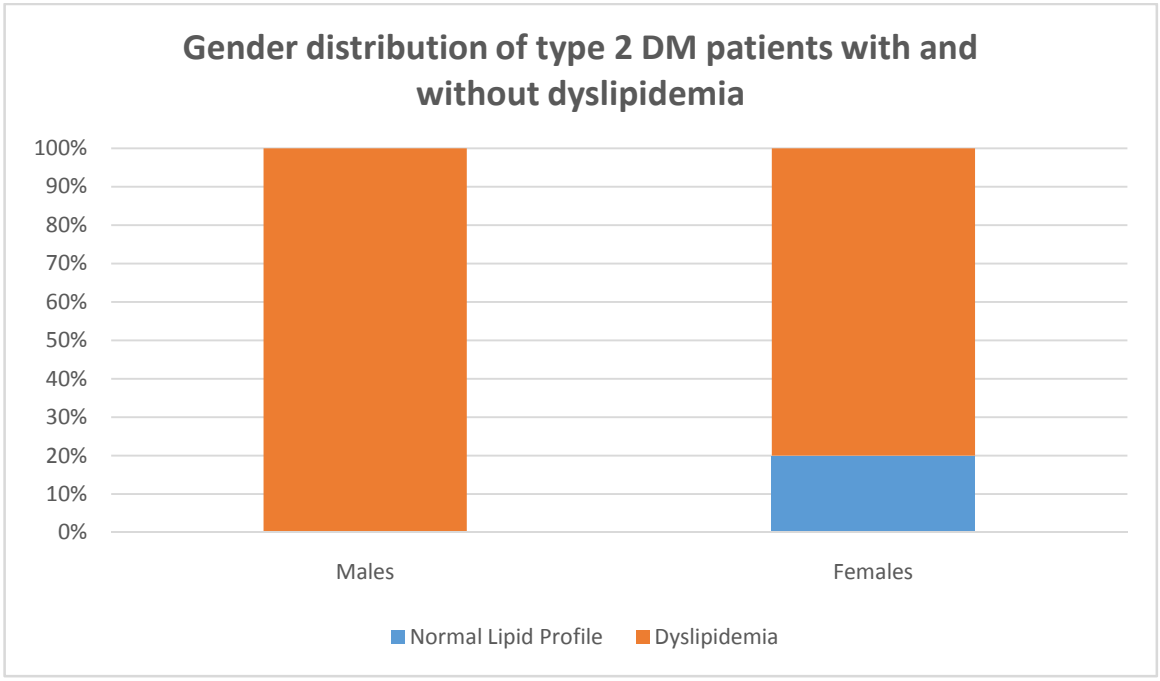


TABLE 8.2 – GENDER DISTRIBUTION OF DYSLIPEDEMIA IN PATIENTS WITH TYPE 2 DM AND SUBCLINICAL HYPOTHYROIDISM

	Normal lipid profile	Dyslipidemia	Total
Males	0	9 (100%)	9 (100%)
Females	3 (20%)	12 (80%)	15
Total	3	21	24

CHART 8.2 – GENDER DISTRIBUTION OF DYSLIPIDEMIA IN PATIENTS WITH TYPE 2 DM AND SUBCLINICAL HYPOTHYROIDISM



DISCUSSION

DISCUSSION

The study was done in two hundred patients in Rajiv Gandhi Government General Hospital at the Institute of Internal Medicine. Cases were obtained from both inpatient as well as outpatient department. Cases were patients who were known to have Type 2 Diabetes Mellitus for any duration, and aged above 40 years. Fasting thyroid function tests, Fasting Lipid profile and Serum Glycated Haemoglobin was taken for all patients. Fasting thyroid function tests included serum free T3, free T4 and serum thyrotropin (TSH). Fasting lipid profile included Total cholesterol, low density lipoprotein cholesterol (LDL-cholesterol), high density lipoprotein cholesterol (HDL-cholesterol) and serum triglyceride levels. Free T4 and serum TSH were obtained via chemiluminescence assay. Lipid profile was obtained via standard laboratory assays for the same. Glycated haemoglobin values were obtained via high performance liquid chromatography. Patients were also subjected to liver function tests, renal function tests, complete blood count and all those who had an abnormality in these tests were excluded. Due to lack of studies correlating thyroid function and microvascular complications of Diabetes, patients with overt diabetic neuropathy, retinopathy and nephropathy were excluded from the study.

Prevalence of Subclinical Hypothyroidism

Out of 200 individuals included in the study 168 patients had normal thyroid function. This accounted for 86 percent of the cases. Twenty four individuals had a biochemical diagnosis of Subclinical Hypothyroidism. This accounted to about 12 %. Eight individuals had overt Hypothyroidism, diagnosed as an elevated thyrotropin level with a suppressed free T4 level as well. The p value was 0.025. The study showed a statistically significant incidence of Subclinical Hypothyroidism in patients with type 2 Diabetes.

The study showed an incidence of Subclinical Hypothyroidism that was similar to other studies. The study correlated best with a trial performed in Greece in 2010, where a prevalence of SCHT was 12.4%, as compared to 12 % in our study[61].

This study had a higher rate of Subclinical Hypothyroidism compared to few other studies. In the study in Segovia, Spain, it was 10.7%[47], and in the Fremantle Diabetes Trial, it was 8.8%. The study however did not include testing the patients for Anti thyroid antibodies (Antibodies to thyroid peroxidase enzyme) that was done in all the studies mentioned above.

Age Distribution

The individuals included in the study were separated based on groups into ages 40 – 45 years, 46 – 55 years, 56 – 65 years, 66 to 75 years and more than 75 years. It was observed that majority of the members included in the study fell into the age groups 46 to 55 years (84 out of 200, 42 percent), followed by 56 to 65 years (50 out of 200, 25 percent). The age group that had the minimum members was >75 years group, which consisted of 6 out of 200 (3 percent). However, even though the overall individuals included in the study was higher in the 46 to 55 years age group, the incidence of SCHT was higher in the 56 to 65 years group, with 13 individuals in this group having SCHT (26 percent in the age group). In the 46 to 55 years age group, the incidence of SCHT was 6 out of 84 (7.1 percent in the age group). However, the stratification of the observed individuals based on age did not prove to be of any statistical significance (p value 0.450). The average age of individuals with type 2 DM and a normal thyroid function test was 55.21 years, and average age of those who had type 2 DM and SCHT was 55.54 years.

The age stratification was not significant statistically in the Greece trial as well (p value 0.17)[61]. The average age of diabetic individuals with an abnormal thyroid function was 65.54 years, compared to 67.12 years in diabetic individuals with a normal thyroid function. There was also no significant difference in age in the Fremantle Diabetes Study as well. One

study that showed a statistically significant increase in the incidence of SCHT in Type 2 DM was by Kim et al, where the mean age of patients with a normal thyroid status was 57.9 years and those with SCHT was 61.8 years[64].

In Karnataka, India, a study in a medical college on hundred and fifteen individuals was performed and the mean age was similar to ours – 54.83 years[65]. Another study in South India had a mean age of 58.77 years. These two studies had similar age group stratification which possibly indicates that the incidence of SCHT in Type 2 DM in India may occur at a slightly younger age. However more trials are necessary to substantiate this observation.

Gender Distribution

The participants of the study were divided based on the gender and it was observed that 92 individuals out of 200 were males (46 percent), and 108 out of 200 females (54 percent). Among the male population, 80 individuals (87 percent males) had normal thyroid function, 9 had SCHT (9.8 percent) and 3 had overt HT (3.3 percent). Among the females, 88 individuals (81.5 percent females) had normal thyroid function, 15 had SCHT (13.9 percent) and 5 had overt HT (4.6 percent). Among patients with SCHT, 9 of the individuals were males, accounting to 37.5% individuals. The rest 15 out of 24 patients were females, making up 62.5% of the population. Among patients with overt Hypothyroidism, 3 out of 8 individuals were males (37.3

percent) and the other five are males (62.5 percent of the population). The incidence of SCHT in patients with type 2 DM is clearly more prominent in females, and this observation has been statistically significant in the study (p = 0.045).

Most of the trials conducted for similar aims have noticed an almost similar pattern of distribution of patients. The Fremantle Diabetes Study was done exclusively in females and had a lower prevalence of SCHT of about 8.7% compared to 13.9 percent in our study[69]. Chen HS et al revealed in a study in Taiwan that SCHT was 5.3% in males and 8.4% in females with type 2 DM[68]. In the Greek study, the prevalence was much higher at 18.5% in females, and 5.5 percent in males, the male prevalence being almost comparable to other studies[61].

In the Indian population, only one significant study evaluated the gender distribution of Subclinical Hypothyroidism in type 2 DM, with the prevalence being 22 percent in females and 4 percent in males, the female prevalence being much higher than in the present study.

Subclinical Hypothyroidism and glycemic profile

Individuals were grouped according to Glycated haemoglobin levels (HbA1C) into HbA1C <7%, 7 to 8 %, 8 – 9 %, 9 – 10 %, and > 10 %, and

normal and abnormal TSH values into 0.3 – 5.5 microIU/mL, 5.5 to 6.5 and >6.5 microIU/mL.

Most patients with a normal TSH value had an HbA1C below 8% (107 out of 168 individuals, making up 63.7% euthyroid individuals). Only 18 out of 168 individuals (10.7 percent) had very high HbA1C levels more than 10% and yet had a normal thyroid function test.

Among individuals with increased TSH values, 40.63 percent of them had higher HbA1C more than 10 %, the prevalence in this group increasing as TSH increased (9 out of 20 [45 percent] in TSH > 6.5 microIU/mL group compared to 4 out of 12 [33.3 percent] in the group with TSH between 5.5 to 6.5 microIU/mL). However, this was found to be statistically insignificant (p value 0.25).

The mean HbA1C value in diabetic individuals without thyroid abnormalities was 7.93 %. The mean HbA1C value in individuals with type 2 DM and Subclinical Hypothyroidism was 8.53 %. The mean HbA1C value in individuals with type 2 DM and Overt Hypothyroidism was 8.085%. The average HbA1C in individuals with an abnormal thyroid function was 8.31 %, a value higher than those with normal thyroid function.

Most of the studies comparing Subclinical Hypothyroidism and type 2 Diabetes could not come up with a statistically significant correlation

between level of thyroid dysfunction and glycemic profile. In contrast, the Greek study on type 2 DM patients showed a reduced HbA1C level in patients with coexisting Hypothyroidism (7.38% compared to 7.81%) although this was statistically insignificant[61]. The same observation was made by Kim et al in Taiwan, with a mean HbA1C of 8.8 and 8.4% in euthyroid and hypothyroid diabetic individuals respectively[67]. The variations in the above observations and the absence of any significant findings is probably due to the multiple mechanisms by which Hypothyroidism can decrease as well as increase the blood glucose values.

Duration of Diabetes and Thyroid Dysfunction

Participants were divided into 5 groups according to the duration of Diabetes from the detection to present, into less than 1 year, 1 to 4 years, 4 to 7 years, 7 to 10 years, and more than 10 years. Participants were also grouped according to TSH values. It was observed that there was no significant correlation between thyroid dysfunction and the duration of Diabetes (p value 0.45). Majority of the individuals had a duration of Diabetes below 7 years, regardless of whether their thyrotropin levels were high or not. In patients with TSH levels below 5.5 microIU/mL, 52 participants (30.9 percent of euthyroid diabetics) had duration of Diabetes more than ten years, some even had duration more than 20 years. On the other hand, only 6 out of 32 individuals (18.75 percent) with a TSH level above 5.5 microIU/mL had

duration of Diabetes more than 10 years. In individuals with type 2 DM and SCHT, the duration of Diabetes was almost equally stratified, majority (30 percent) of the cases fell into the 4 to 7 years group.

The mean duration of Diabetes among diabetic individuals with normal thyroid status was 7.28 years, the mean duration among those with SCHT was 5.72 years. So there is no relation between the prevalence of SCHT and the duration of Diabetes. This variation in the average values is possibly because of the wide range of values considered. The median value, however, in both the euthyroid group and in the group with SCHT, was 6 years.

In the study in Greece, the mean duration was 14.28 and 14.64 years among individuals with and without thyroid dysfunction respectively[61]. There was no significance in the duration of Diabetes regarding the prevalence of thyroid dysfunction. In India, in a study in Karnataka, the mean duration of Diabetes in the SCHT group was 6.15 years[67]. Two studies in the South East Asian Region had a mean duration of Diabetes of 8.9 years and 8.3 years[66]. The above difference may be due to the differences in the mean age of SCH patients in the studies as well – 55.54 in the present study versus 61.7 years in the study by Kim et al versus 61 years in the study by Yang et al[66].

Total Cholesterol and Subclinical Hypothyroidism

The upper limit of normal of serum total cholesterol was taken as 200 mg/dL as per the standards in the biochemistry department. Based on this, participants were separated into two groups – one with a normal (<200 mg/dL) and abnormal (>200 mg/dL) total cholesterol. In patients with Type 2 DM and normal thyroid, 30.4 percent (51 out of 168) had an abnormal Total cholesterol, whereas in patients with Subclinical Hypothyroidism 45.9 percent (11 out of 24) had an abnormal total cholesterol. The mean values of total cholesterol in the euthyroid group and the SCHT group were 181.9 mg/dl and 189.17 mg/dl respectively. Although the percentage of individuals with a higher cholesterol level was more in the SCHT group, the correlation was statistically not significant.

In the study in Greece, it was observed that diabetic patients with thyroid dysfunction had a better lipid profile[61]. Mean total cholesterol values were 199.8 and 207.24 in the groups with and without thyroid dysfunction respectively. Satvic et al found a higher mean total cholesterol value in patients with SCHT and Diabetes type 2 but could not elicit any significant correlation between the two. The same findings were observed in a trial by Kim et al[67].

However, in a study conducted in Western Australia, patients with SCHT had significantly higher total cholesterol levels than euthyroid

individuals (mean 243.62 versus 224.28, p value <0.001)[69]. In a trial by Gray et al, it was observed that diabetic individuals with an increased TSH without clinical signs of thyroid failure had a significantly higher mean serum total cholesterol concentration (262.95 mg/dl in elevated TSH group versus 232.02 mg/dl in normal TSH group; p value 0.025) after matching for age and sex.

There are studies performed to demonstrate the effect of treatment of SCHT with thyroid hormone replacement therapy. Ineck et al performed a trial in USA, and they observed that therapy with l-thyroxine reduced the total cholesterol levels[70]. In the current study, all 11 SCHT participants who had an elevated total cholesterol were already taking statin therapy, so it would be inappropriate to study the effect of replacement therapy on serum lipids in these patients.

Low Density Lipoprotein (LDL) Cholesterol and Subclinical Hypothyroidism

The upper limit of normal of serum LDL cholesterol as per the standards in department of Biochemistry was taken as 100 mg/dL. Participants were grouped into those having normal and abnormal serum LDL cholesterol levels (<100 mg/dL and >100 mg/dL respectively). The total number of participants with an abnormal serum LDL cholesterol was 105 out of 200. Fifty three percent of individuals with normal thyroid function (89 out of 168) had an elevated LDL cholesterol, versus 66.7 percent in patients with

SCHT (16 out of 24) and 37.5 percent in those with overt Hypothyroidism (3 out of 8). The p value was 0.094 and there was no statistical significance between thyroid status and LDL cholesterol. The mean LDL cholesterol values were 108.39 mg/dL, 121.15 mg/dL and 108.9 mg/dL in normal thyroid, subclinical hypothyroid, and overt hypothyroid groups respectively. There was a significantly higher prevalence as well as a higher average value in those patients with both type 2 DM and SCHT.

Papazafiropoulou et al found an improved LDL cholesterol profile in diabetic individuals with abnormal thyroid function which was statistically significant as well (114.94 in dysthyroid individuals versus 128.05 in euthyroid p value 0.001)[61]. Satvic et al and Kim et al found a similar LDL profile as compared to the present study but could not arrive at a significant correlation[66, 67]. In the Fremantle Diabetes study, a significantly higher serum LDL level was observed in the SCHT group than in euthyroid individuals (mean 166.28 versus 135.35, p value <0.001)[69]. Levothyroxine therapy reduced serum LDL cholesterol levels in a group of SCHT patients observed by Ineck et al[70]. Effects of therapy, however, was not studied in the present study.

High density lipoprotein (HDL) cholesterol and Subclinical Hypothyroidism

The normal limits of HDL cholesterol was set as more than 40 mg/dL. Participants were grouped into those with low and normal HDL cholesterol levels (less than 40 and more than 40 mg/dL respectively). The prevalence of patients with a low HDL cholesterol was 39.3 percent in normal thyroid status group (66 out of 168), 50 percent in SCHT group (12 out of 24) and 62.5 percent in the overt Hypothyroidism cases (5 out of 8). This showed a rising trend in the prevalence of abnormal HDL cholesterol levels from normal to subclinical hypothyroid to overt hypothyroid cases. However, this trend was shown to be statistically insignificant (p value 0.632). The mean values of HDL cholesterol were 42.44, 42.45 and 39.3 in normal thyroid individual, individuals with SCHT and those with OHT respectively.

Satvic et al compared the mean values of serum HDL cholesterol in euthyroid and SCHT patients with Diabetes mellitus and found a lower average value in SCHT (38.14 versus 40.06) but was insignificant[66]. Similar observations were made by Kim et al[67]. The Fremantle Diabetes study on diabetic women showed a lower mean HDL cholesterol in the patients with higher serum thyrotropin levels (43.7 versus 45.24) but was found to be statistically insignificant[69]. In Greece, however, the mean HDL cholesterol was above normal limits in both dysthyroid and euthyroid groups, but the

diabetics with abnormal thyroid function had a higher HDL cholesterol (51.7 versus 47.35) which was statistically significant[61].

Serum Triglyceride levels and Subclinical Hypothyroidism

The normal value of serum triglyceride levels was taken to be below 150 mg/dL as per standard laboratory definitions. However, there is an increased risk of adverse cardiac and vascular outcomes with a triglyceride level above 100 mg/dL. So participants were divided into 3 groups - < 100 mg/dL, 100 – 150 mg/dL and >150 mg/dL.

Among individuals with type 2 DM and normal thyroid status, 79 of them (47%) had serum triglyceride levels less than 100 mg/dl, 66(39.3 percent) between 100 to 150 mg/dl and only 23 (13.7 percent) had an increased triglyceride level more than 150 mg/dl. Among those with SCHT, all patients had triglyceride levels above 100 mg/dl, with 5 patients having levels between 100 and 150 mg/dl (20.8%) and the majority, 19 members (79.2 percent) having elevated levels of triglycerides >150 mg/dl. In the members with overt Hypothyroidism, 2 (25 percent) had levels below 100 mg/dl, and 5 (62.5 percent) had levels above 150 mg/dl. Only 1 patient had levels between 100 to 150 mg/dl. The observation that elevated levels of triglycerides are seen in the group with Subclinical Hypothyroidism was statistically relevant (p value 0.008). The mean values of serum triglyceride

levels were 151.3, 184.4 and 148.3 mg/dL in euthyroid, SCHT and Overt Hypothyroidism patients respectively.

In the Subclinical Hypothyroidism group, it was shown that majority of the patients with an elevated triglyceride level were females (11 out of 19, 57 percent), and 13 out of 19 members affected (68.42 percent) were in the age groups 50 to 70 years. None of the members with elevated triglyceride levels were above 70 years of age, and an increasing trend in prevalence of hypertriglyceridemia with age could not be demonstrated. This may be because of the small sample size that was studied for lipid profiles in SCHT group.

In the trial conducted by Satvic et al, the mean triglyceride level was 178 mg/dl in the SCHT group and 151 in the Euthyroid group, but the difference in the levels was statistically insignificant (p value 0.185)[66]. Kim et al found a lower mean triglyceride value (195 mg/dl in normal thyroid individuals versus 182 mg/dl in SCHT individuals) in SCHT patients compared to diabetics with normal thyroid function[67]. The Fremantle Diabetes Study and trials conducted by Papazafiropoulou et al also could not elicit a significant correlation between presence of SCHT and hypertriglyceridemia[61, 69].

Overall, dyslipidemia (any abnormality in the serum total cholesterol, serum HDL cholesterol, serum LDL cholesterol and serum triglycerides) was

more prevalent in females than males. 153 participants had dyslipidemia (76.5 percent) and dyslipidemia was present in 79.6 % females (86 out of 108) and 72.8% of males (67 out of 92). The prevalence in females, was not statistically significant (p value 0.924). In the patients with both type 2 DM and Subclinical Hypothyroidism, all the males had evidence of some form of dyslipidemia (9 males, 100%) and 80% females had dyslipidemia (12 out of 15 females).

Several studies have demonstrated an increased prevalence of dyslipidemiain females with type 2 Diabetes. However, in the trial in Greece conducted on diabetics, dyslipidemia was more common in males than females, and this prevalence was more prominent in patients with coexisting SCHT. The observation was, however, statistically insignificant. In the study conducted by Satvic et al, there was a higher prevalence of dyslipidemia in females compared to males in both the groups, that is in patients with only type 2 Diabetes, and in patients with both type 2 DM and Subclinical Hypothyroidism.

CONCLUSION

CONCLUSION

1. There is a significant incidence of Subclinical Hypothyroidism among individuals having Type 2 Diabetes Mellitus.
2. The incidence of Subclinical Hypothyroidism among individuals having Type 2 Diabetes Mellitus is significantly higher in females than males.
3. There is no significant relationship between incidence of Subclinical Hypothyroidism in Type 2 Diabetes and age, and duration of Diabetes.
4. There is no significant effect of the presence of Subclinical Hypothyroidism in patients with type 2 Diabetes Mellitus over HbA1C (Glycemic profile)
5. There is no significant effect of the presence of Subclinical Hypothyroidism in patients with Type 2 Diabetes Mellitus over Total cholesterol, LDL cholesterol, and HDL cholesterol levels.
6. Patients with Type 2 Diabetes Mellitus and Subclinical Hypothyroidism had a significantly higher prevalence of hypertriglyceridemia compared to those with a normal thyroid function, and the mean triglyceride value was significantly higher in diabetic individuals who had coexisting Subclinical Hypothyroidism.

LIMITATIONS

LIMITATIONS

1. The presence of Anti – TPO antibodies (antibodies to thyroid peroxidase) was not included in the study, which is shown to have significantly higher levels in patients with Subclinical Hypothyroidism in many studies
2. The presence and absence of diabetic complications in patients with Subclinical Hypothyroidism was not analysed.
3. There was a lack of similar studies performed in India to compare and contrast.

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BIBLIOGRAPHY

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ANNEXURES

QUESTIONNAIRE

INCIDENCE OF SUBCLINICAL HYPOTHYROIDISM IN TYPE 2 DIABETES MELLITUS AND ITS EFFECTS ON LIPID PROFILE AND HBA1C

Name: Age: Sex: IP Number:

Presenting Complaints:

Duration of Diabetes:

Presence of vascular complications of diabetes

Nephropathy: Neuropathy:

Retinopathy: CAD:

Peripheral vascular disease: Cerebrovascular disease:

Presence of symptoms of hypothyroidism:

Current drugs taken:

Drugs for Diabetes:

Other drugs currently taking:

Past h/o thyroid disease: Family h/o thyroid disease:

Recent Thyroid function tests (if any):

Menstrual history (if female):

Examination

PR: BP:

Neck Swelling: Examination of skin:

CVS:

RS:

P/A:

CNS:

Investigations:

1. Complete Blood Count:

Hb:	TC:	DC: P L E M
ESR:	PCV:	Platelet:

2. Renal Function Tests:

S. Urea:	S.Creatinine:
S. Na:	S. K:

3. FBS:

4. PPBS

5. Thyroid Function Tests:

F T3:

F T4:

TSH:

6. Complete Lipid Profile:

S. Cholesterol:	S. Triglycerides:
S. LDL Cholesterol:	S. HDL Cholesterol

7. HbA1C:

8. Others (if any):

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Arvind Krishnakumar,
Post Graduate,
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. Arvind Krishnakumar,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Incidence of subclinical hypothyroidism in patients with type 2 Diabetes mellitus and its effects on lipid profile and HbA1C"** No.26062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

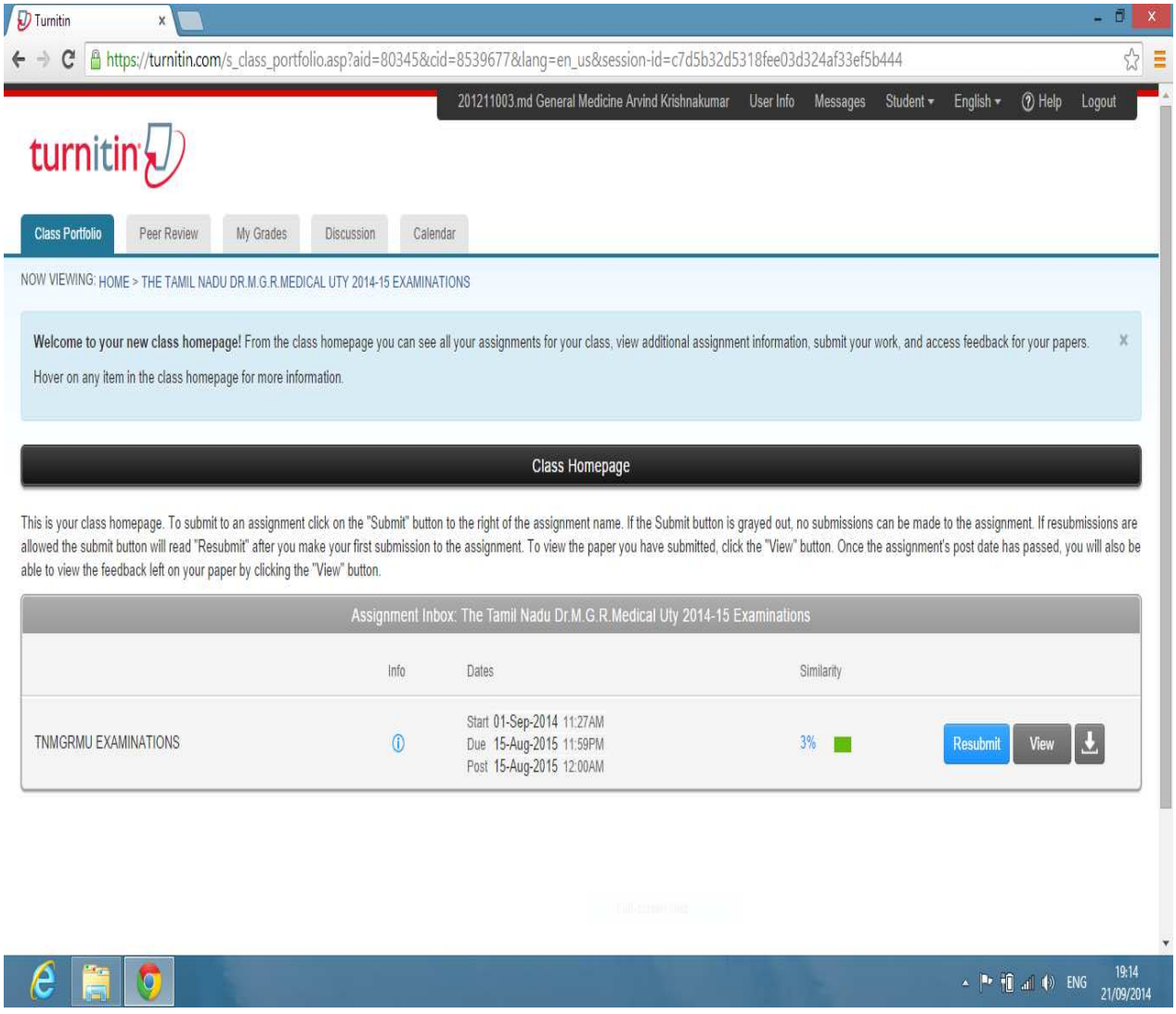
Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

PLAGIARISM SCREEN SHOT (TURNITIN)



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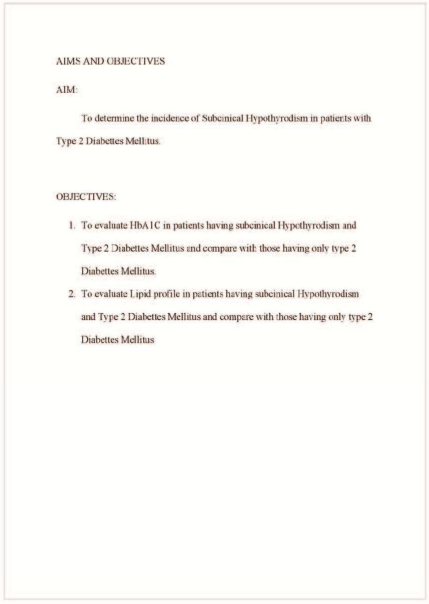

AIMS AND OBJECTIVES

AIM:

To determine the incidence of Subcinical Hypothyrodism in patients with Type 2 Diabettes Mellitus.

OBJECTIVES:

1. To evaluate HbA1C in patients having subcinical Hypothyrodism and Type 2 Diabettes Mellitus and compare with those having only type 2 Diabettes Mellitus.
2. To evaluate Lipid profile in patients having subcinical Hypothyrodism and Type 2 Diabettes Mellitus and compare with those having only type 2 Diabettes Mellitus

INFORMATION SHEET

We are conducting a study on '**Incidence of subclinical hypothyroidism in patients with type 2 diabetes mellitus and its effects on lipid profile and HbA1C**' among patients in Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the correlation of subclinical hypothyroidism and diabetic patients with respect to the glycemic control and lipid profile. We are selecting certain cases, and if you are eligible, 2 samples of 3 cc blood will be collected in fasting state in the morning and sent for investigations. These tests do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment

Signature of the Investigator Signature of the Participant

Date:

Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனைக்கு வரும் சர்க்கரை நோயாளிகளிடம் இரத்தப் பரிசோதனை செய்யப்பட்டு அதில் தைராய்டு ஹார்மோன் கோளாறுகள் பற்றி ஒரு ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

சர்க்கரை நோயாளிகளுக்கு தைராய்டு குறைபாடுகள் அதிக அளவில் ஏற்படுகின்றன. கொழுப்புச் சத்தின் அளவும் கூடியிருக்க வாய்ப்புகள் இருக்கின்றன. இவை ஆராய்வதே இந்த ஆராய்ச்சின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய இரத்தம் பரிசோதனை செய்யப்பட்டு அதன் தகவல்கைள ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Title	:	Incidence of subclinical hypothyroidism in patients with type 2 diabetes mellitus and its effects on lipid profile and HbA1C
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ❑

Signature/thumb impression

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name:

Dr. Arvind Krishnakumar

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

சர்க்கரை நோயாளிகளின் தைராய்டு ஹார்மோன் குறைபாடுகள் பற்றிய ஆராய்**ச்சி**

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் தைராய்டு ஹார்மோன் அளவு, கொழுப்புச்சத்து அளவு, HbA1c அளவு ஆகியவை நான் பரிசோதனை செய்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் நான் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் சர்க்கரை நோயாளிகளுக்கு ஏற்படும் தைராய்டு ஹார்மோன் குறைபாடுகள் குறித்த இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல்தாளைப் பெற்றுக்கொண்டேன்.

நான் இந்த ஆய்வின் போது சந்தேகம் இருந்தால் ஆராய்ச்சியாளரை தொடர்பு கொள்ள வேண்டும் என்பதை அறிவேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்

MASTER CHART

S. NO	CASE	AGE	GENDER	DURATION	HbA1C	FREE T3	FREE T4	TSH	T CHOL	HDL	LDL	TGL
Normal	ABC				<6.5%	2 - 4.4 pg/ ml	0.7 - 1.8 ng/dL	0.3 - 5.5microIU/mL	< 200 mg/dL	> 40 mg/dL	< 100 mg/dL	<150 mg/dL
1	Shaliga	50	M	5 years	6.8	1.9	1.8	1.6	174	44	107	112
2	Chitra	56	F	7 years	10.8	2	0.8	7.6	201	34	161	274
3	Sumithra	45	F	4 years	7.3	3	1	1.4	173	52	103	91
4	Rukumani	52	F	2 years	11	2.62	0.82	5.2	146	50	82	139
5	Usha Kumari	48	F	1 Year	6	2.32	0.64	9.325	164	35	122	95
6	Sudha	46	F	7 Years	8.2	4	1.2	1.4	154	39	96	174
7	Meyappan	50	M	8 years	6.5	3.2	0.97	1.2	147	34	88	91
8	Ramalingam	60	M	6 years	7.7	3.33	1.24	5.99	152	37	96	202
9	Malathy	49	F	15 years	6.7	3.1	1.4	2.08	123	31	70	110
10	Chandrasekar	57	M	3 Years	10.3	3.24	1.3	6.38	176	44	98	169
11	Suguna	46	F	2 years	6.8	2.8	1.23	3.1	268	40	202	124
12	fathima	54	F	4 years	6.5	2.85	0.8	1	172	38	102	154
13	Raja	43	M	3 Years	8.04	3.24	0.95	2.14	111	38.3	55	88
14	Vijayalakshmi	65	F	10 Years	8	2.23	0.9	5.7	161	33	103	125

15	Abdul Razak	49	M	4 years	8.2	3.8	1.61	0.78	260	52	106	210
16	Divya	45	F	3 Years	11.1	2.75	0.61	2.32	283	61	197	123
17	Vanaja	64	F	12 Years	7	3.22	1.03	4.81	177	44	109	121
18	Vishwanathan	62	M	5 years	5.6	2.73	0.82	11.63	252	27	189	181
19	Dennis	50	M	5 years	9.5	3	0.97	3.053	331	51	228	339
20	Salahudeen	78	M	15 years	7.8	2.7	0.98	1.86	168	45	88	173
21	Kalyani	65	F	6 years	5.63	2.45	1.01	3.145	165	48.2	101.8	78
22	Ramalingam	67	M	7 years	7.3	3.05	1.04	1.626	204	37.4	137	148
23	Aneesh	57	M	7 years	9.27	2.75	1.08	3.916	235	37.1	146	259
24	Sriram	45	M	1 Year	6.32	2.35	1.4	4.8	145	55.3	67.9	109
25	Mary stella	65	F	4 years	9.1	3.2	1.04	0.89	198	43	97	154
26	Kannan	47	M	6 months	6.7	3.1	1.16	0.73	160	47	86	123
27	Rajendran	46	M	2 years	7.2	3.21	1.04	3.17	153	28	90	165
28	Ashok	57	M	3 years	5.9	4.2	1.33	1.56	159	29	91	177
29	Vishalakshi	73	F	12 years	7.7	3.92	0.87	2.46	178	43	98	164
30	Amaravathy	55	F	2 years	11.8	2.12	0.76	4.75	204	29	86	190
31	Shiva	47	M	2 years	10.58	2.4	0.68	5.65	180	46.2	98	169
32	Kousalya	49	F	1 Year	6.7	2.81	0.98	1.342	140	44.9	70	123
33	Mary	52	F	5 years	8.8	4.2	1.95	0.3	178	47	96	154
34	Nagavalli	45	F	6 months	8.7	2.2	1	5.56	202	38	124	178
35	Amulu	42	F	4 years	13.6	1.73	0.7	1.3	240	45	132	184
36	Kokila	53	F	12 years	6.6	2.35	0.998	5.25	171	34	99.2	189

37	Rajesh	48	M	3 years	6.9	2.4	0.9	3.46	177	44	104	147
38	Ram Mohan	51	M	4 years	8.1	3.2	1.7	1.97	159	45	89	129
39	Gangadhar	59	M	2 years	7.9	0.81	1.65	4.84	238	54	102	117
40	Valarmathi	44	F	6 years	8.09	2.78	1.15	2.061	211	43.1	137	154
41	Chakrapani	73	M	20 years	7.31	2.19	1.14	2.596	137	33.5	83	83
42	Thilagavathy	60	M	12 years	8.6	2.47	1.09	3.35	201	37	110	254
43	Kamala	71	F	14 years	6.85	2.4	1.3	3.776	129	42.6	71	73
44	Mansooriya	50	F	4 years	6.7	2.89	1.24	2.35	165	33	103	145
45	Raju	72	M	12 years	7.2	2.5	1.23	2.841	160	45	88	137
46	Safiya	49	F	2 years	7.4	4.1	1.35	6.6	232	46	156	161
47	Lilly	61	F	10 years	8.9	2.81	1.78	1.44	224	44	147	168
48	Sundaraswami	62	F	10 years	7.8	3.4	2.067	2.9	200	40	128	160
49	Muthuvara Ganapathi	65	F	13 years	6.6	2.95	1.45	5.13	141	66	60	73
50	Jaibunisha	54	F	4 years	12.1	3.15	1.31	3.06	250	40	163	154
51	Muhamada bee	53	F	2 years	6.6	2.35	0.75	1.56	170	36	104	145
52	Karthik	52	M	5 years	6.76	2	1.7	1.53	175	43	107	113
53	Usha	57	F	7 years	10.75	1.8	0.76	6.5	205	37	172	250
54	Aishwarya	45	F	3 years	7.5	3.24	1.2	1.6	173	55	104	95
55	Veena	53	F	2 years	10.5	2.54	0.78	5.1	150	48	87	140
56	Shoba	49	F	5 years	6	2.34	0.65	7.6	168	37	125	98
57	Radhika	46	F	7 years	8.1	3.8	1.3	3.5	157	39	100	180

58	Subramanian	50	M	8 years	6.6	3	0.88	1.5	143	34	92	97
59	Vikram	60	M	6 years	7.6	3.4	1.27	5.87	160	39	105	207
60	Malini	48	F	12 years	6.8	3	1.3	2.01	125	33	72	123
61	Suganya	47	F	3 years	6.7	2.73	1.34	3.4	272	43	198	157
62	Siddarth	56	M	4 years	9.8	3.12	1.6	5.72	182	47	98	173
63	Raju	43	M	1 year	7.9	3.7	0.93	2.14	112	37	70	120
64	Ambika	62	F	11 years	8.3	2.7	0.73	5.34	164	37	106	135
65	Hussain	51	M	6 years	8.4	3.7	1.72	3.5	262	54	108	213
66	Sneha	43	F	2 years	7.2	2.6	0.85	5.2	275	45	185	190
67	Arun	65	M	8 years	5.8	2.1	0.56	9.7	247	33	174	180
68	Jalaja	61	F	10 years	7.2	3.12	1.1	4.3	175	42	102	128
69	Savio	51	M	2 years	8.9	2.7	0.78	3.24	280	54	190	275
70	Nawaf Ali	75	M	20 years	7.5	2.1	0.81	2.24	165	45	90	179
71	Varsha	64	F	7 years	5.7	2.32	1.3	3.45	190	47	102	82
72	Lingam	62	M	3 years	7.8	3.1	1.11	2.43	202	36	122	150
73	Aparna	58	F	6 years	8.7	2.73	1.24	4.7	210	39	102	243
74	Rohit	47	M	2 years	6.4	2.35	1.6	4.3	145	56	78	109
75	Teena	60	F	4 years	9.2	2.7	1.3	3.1	150	45	83	143
76	Nandu	48	M	1 year	6.5	3.12	1.2	0.8	162	45	88	130
77	Rajasekar	47	M	3 years	7.1	3.2	1.1	3.24	160	30	92	168
78	Ashwin	58	M	3 years	6	4.1	1.35	1.65	169	35	94	174
79	Vineetha	72	F	11 years	7.4	3.82	0.89	2.64	187	41	89	146

80	Vasuki	54	F	2 years	10.8	2.2	0.96	4.57	198	32	89	192
81	Krishna	49	M	3 years	9.8	2.3	0.89	1.43	145	46	73	132
82	Supraja	53	F	5 years	6.8	2.72	0.78	1.423	150	43	68	124
83	Monisha	54	F	6 years	8.6	4.6	1.87	0.3	178	47	96	154
84	Valli	47	F	4 years	8.8	2.4	1.4	5.43	202	38	124	178
85	Anula	44	F	4 years	12	1.87	0.8	7.6	240	45	132	184
86	kasthuri	54	F	7 years	6.9	2.56	1.12	5.3	179	37	102	196
87	rakesh	45	M	4 years	7.2	2.7	1.04	3.42	189	44	98	167
88	Ram Prakash	54	M	3 years	8.2	2.78	1.78	3.32	164	47	76	139
89	ganesh	45	M	2 years	7.5	0.98	1.65	4.83	234	56	104	149
90	Ashwathy	47	M	5 years	8.09	2.78	1.15	2.061	211	43.1	139	160
91	suresh	72	M	13 years	7.32	2.19	1.15	2.576	138	37	92	97
92	roopa	58	F	12 years	8.6	2.47	1.09	3.35	201	37	110	254
93	Sasikala	70	F	13 years	6.85	2.32	1.2	3.776	129	42.6	71	73
94	archana	50	F	3 years	7.2	2.72	1.32	2.53	170	38	108	150
95	ramesh	70	M	12 years	7.4	2.8	1.76	2.78	190	50	108	157
96	Nargis	49	F	3 years	7.6	3.9	1.78	5.7	242	47	176	176
97	Anne	72	F	10 years	8.7	2.32	1.87	1.54	224	45	155	176
98	Shweta	66	F	10 years	7.9	3.6	2.26	3.2	178	43	129	170
99	Balakrishnan	66	M	6 years	6.7	2.97	0.82	1.98	141	66	60	73
100	zubeida	53	F	3 years	11.1	3.89	1.43	3.74	236	43	165	150
101	Saravanan	47	M	6 years	7	1.7	2.1	3.125	170	50	90	135

102	Sujatha	53	F	8 years	10	2.2	1.6	5.82	166	34	143	240
103	Vaidehi	27	F	5 years	7.3	3.1	1.2	1.1	163	48	93	93
104	amreen	50	F	4 years	10	2.8	0.6	5.54	147	60	80	142
105	devi	46	F	2years	7	2.4	0.65	1	170	37	112	98
106	mallika	48	F	8years	9	4	1.4	1.5	160	36	90	167
107	arasar	48	M	8 years	6.7	3	1	1.3	150	30	90	90
108	Ashok	60	M	7 years	7.2	3.4	1.34	5.7	156	38	102	201
109	gowri	50	F	4 years	6.5	3	1.2	2	130	42	70	126
110	raja	54	M	3 Years	11	2.7	1.2	5.23	180	38	100	170
111	Sukanya	47	F	2 years	6.8	2.8	1.23	3.1	268	40	202	124
112	jayalakshmi	56	F	2 years	7.3	2.78	0.87	2.09	177	39	105	180
113	duraiarasan	40	M	4years	8	3.3	1	3	130	42	60	100
114	lilly	65	F	6years	7	2.5	2	5.2	170	38	108	140
115	srinivasan	52	M	5years	7	4	1.8	1	189	52	110	220
116	rukmini	45	F	4years	12	2.9	0.7	2	200	71	190	163
117	vani	60	F	10 years	7	3	2	4.5	167	45	110	139
118	vikram	59	M	6 years	5.9	3	1	1.2	260	34	170	160
119	siva	50	M	7years	10	2.6	1	3	300	50	220	300
120	fahad	75	M	20years	8	3	1	1.86	170	50	90	180
121	kavipriya	60	F	8years	5.63	2.45	1.01	3.145	165	48.2	101.8	78
122	arshad	65	M	6years	7	4	1	1.9	198	37	150	153
123	surya	60	M	8years	8	2.75	1	3.24	200	35	160	230

124	venkatram	43	M	1 Year	6	2.5	2.3	3.5	150	50	70	100
125	malathy	61	F	6years	10	3.8	1.4	0.6	210	38	87	230
126	dheena	46	M	6months	7.1	1.8	2	0.8	170	50	80	144
127	madhesh	44	m	3years	6.5	3	1	4.1	160	37	90	165
128	ratnavel	55	M	4years	6.9	4	3	1.7	165	30	100	190
129	lakshmi	70	F	15years	8	2.6	1.8	3.4	170	38	97	210
130	soundarya	50	F	3years	12	3.4	2.6	4.9	184	45	90	240
131	srinivasan	49	M	3years	11	3.1	2.14	3.8	190	48	100	170
132	snehalatha	50	F	1 Year	7	2.81	1	1.5	154	56	77	180
133	sasikala	50	F	6years	7.2	4	2	0.3	170	42	88	187
134	nalina	46	F	8months	8	2.3	1.4	6.2	212	50	109	240
135	pushpam	44	F	6years	12	1.88	1.7	1.2	149	39	94	143
136	vani	52	F	10years	6.3	3.3	1.2	5.6	150	33	100.6	200
137	ravindran	50	M	3 years	7	2.1	1	4.4	180	48	100	170
138	kannan	55	M	5years	8.4	1.5	1.7	2.3	170	47	88	139
139	prakash	56	M	4years	7	0.81	0.92	6.7	240	77	100	130
140	anusuya	44	F	7years	9	3.4	1.7	2.5	200	44	189	160
141	devaraju	70	M	20 years	8	2.9	1.67	3.2	147	37.5	89	108
142	naveen	60	M	14years	7.9	3.4	1.4	3.35	210	40	117	240
143	nalina	67	F	10years	7.5	2.2	1.24	4.6	140	44	70	117
144	jasbeer	50	F	6years	7	3.5	2.1	2.4	176	44	100	160
145	chandran	77	M	15years	7.6	3	1.33	3.1	180	55	80	140

146	Mohana	47	F	3 Years	8	5.1	1.02	7	223	44	155	176
147	venkatalakshmi	64	F	13years	9	2.6	1.78	1.56	226	40	187	179
148	sarasvathi	60	F	10 years	8.8	3.6	2.7	2.7	198	45	130	180
149	prabha	67	F	12years	7.8	2.95	1.78	5.78	157	77	62	125
150	maragatham	59	F	4years	10.7	3.15	1.56	2.89	200	42	160	189
151	Narayanaswamy	52	M	7 years	7.2	2.76	4.3	0.3	175	47	132	152
152	Madhukar	49	M	10 years	8.5	2.3	1.7	4.32	220	38	110	148
153	Sharon	44	F	3years	6.8	2	1	5.2	160	43	90	140
154	Manmatha	55	M	8years	7.8	3.5	1.5	2.5	190	40	98	135
155	Sharada	65	F	10years	6.7	1.8	0.5	7.22	178	45.2	92.3	189
156	Chandramouli	54	M	12years	10.5	1.3	1	2.3	207	34	125	164
157	Salma	47	F	7years	7.7	2	1.13	6.5	169	41	91	113
158	Mangala	60	F	15years	9.8	2.3	0.3	10.5	231	29	90	157
159	Bharathi	42	F	3years	6.7	2.89	1.23	2.84	165	38	103	145
160	Muthukumaran	44	M	4years	7.2	2.5	1.39	3.1	160	45	88	137
161	Aiyaswamy	70	M	20years	7.4	4.1	1.66	3.45	212	39	154	162
162	Krishnan	60	M	5years	8.7	2.91	1.78	3.44	207	44	154	183
163	Shakunthala	74	F	13years	7.9	3.4	2.067	2.9	200	40	128	160
164	Udayashankar	68	M	18years	6.7	2.9	1.45	5.13	141	66	60	73
165	Jayashree	71	F	16years	12.1	3.8	1.31	4.2	221	39	169	154
166	Kuppuswamy	59	M	8years	6.9	2.4	0.75	1.7	189	36	104	145
167	Backianathan	80	M	25years	8.6	1.9	1.8	2.3	187	43	107	121

168	Soumini	56	F	7 years	10.8	2	0.8	7.6	201	34	161	247
169	Varija	45	F	5years	7.8	2.32	1.9	1.4	173	52	103	91
170	Shoukeena	52	F	2 years	11	4	0.82	5.2	146	50	82	139
171	Sundara	48	F	1 Year	6	3.2	0.64	4.7	164	31	122	95
172	Nalini	46	F	7 Years	8.2	3.33	1.2	1.4	145	39	96	174
173	Micheal	50	M	8 years	6.5	3.2	0.97	1.23	174	34	88	91
174	Syed Pasha	60	M	6 years	7.7	2.98	1.24	5.87	125	31	94	205
175	Merlin	49	F	15 years	6.7	3.1	1.4	2.31	132	37	70	111
176	Shivanna	57	M	3 Years	10.3	3.24	1.3	6.83	167	45	89	156
177	Nagashree	41	F	3years	7	2.66	1.1	4.4	111	41	95	133
178	Mallika	63	F	12years	7.3	2.8	0.98	3.7	164	42	91	140
179	Ashok	51	M	1year	6.5	2.12	2	0.32	190	40	109	138
180	Sunil Kumar	44	M	4years	8.5	2.19	1.87	5	205	36	101	134
181	Raji	47	F	2years	6.8	2	1	4.2	160	43	90	140
182	Obalamma	53	F	8years	6.8	1.8	1.8	1.6	174	44	107	112
183	Shivagami	40	F	5years	10.7	2.1	0.9	4.5	205	39	161	277
184	Ramanathan	84	M	25years	10.5	1.3	1	2.3	207	34	125	164
185	Soundarya	72	F	12years	7.7	2	1.13	6.5	169	41	91	113
186	Thirumala	66	M	16years	9.8	2.3	0.3	4.13	231	29	90	157
187	Joseph	48	M	8years	6.7	3.1	1.23	2.6	156	51	108	145
188	Ravi	45	M	2years	7.2	2.5	1.39	3.1	160	45	88	137
189	Lakshmi	39	F	3years	7.4	4.1	1.66	1.8	211	36	144	158

190	Padmaja	77	F	15years	8.7	2.91	1.67	3.32	214	43	125	183
191	Rajendra	72	M	20years	10.5	1.3	1	2.3	207	34	125	164
192	Shailashree	43	F	14years	7.7	2	1.13	3.4	169	41	91	113
193	Raghuvaran	69	M	9years	9.8	2.3	0.3	10.5	231	29	90	157
194	Sankar	55	M	10years	6.7	2.89	1.23	2.84	165	38	103	145
195	Chandru	46	M	6years	7.2	3.1	1.39	3.1	160	45	88	137
196	Arunachalam	48	M	8years	7.4	2.8	2.3	3.2	212	39	154	162
197	Kaveri	74	F	21years	8.7	2.91	1.67	3.32	214	43	125	183
198	Srinivasulu	62	M	12years	6.8	3	0.97	1.2	147	34	88	91
199	Priyamvatha	81	F	17years	7.2	3	1.24	2.34	152	37	96	202
200	Kishanlal	73	M	15years	6.9	3.3	1.4	2.08	123	31	70	110